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**The Predictive Capacity of a Cognitive Screen: Can the Addenbrooke's
Cognitive Examination - III Predict Early Relapse Following Inpatient
Detoxification in Severe Alcohol Dependence?**



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THESIS ABSTRACT

Background: Alcohol misuse and dependency are major health problems worldwide.

Despite the availability of a number of evidence-based treatments for alcohol-dependency, a large proportion of people relapse following detoxification. The costs to society and the individual are vast, not only economically but in terms of social and interpersonal functioning also. There is a recognised need to understand the factors that contribute to poorer outcomes in this population. Cognitive impairment is one factor that has demonstrated considerable associations with poor outcomes in the wider substance-misuse population.

Aims: This thesis has two sections. The first comprises a systematic review which aimed to present the objective evidence for emotional decision-making deficits in the alcohol dependent population. The second is an empirical study which aimed to establish whether or not relapse can be predicted in a severely alcohol dependent population in the early stages following inpatient detoxification. In addition, a normative dataset for this clinical population using the ACE-III is presented.

Methods: For the systematic review, a structured search of the literature relating to emotional decision-making in alcohol dependent samples was conducted. Iterative application of pre-defined inclusion and exclusion criteria identified eighteen studies for critical review. Quality assessment of these studies was undertaken and validated by means of calculating inter-rater reliability. For the empirical study, two sub-samples of a cross-sectional group of patients being treated for severe alcohol-dependence were examined; one to collate normative data for the ACE-III (N=73) and one to investigate associations between the ACE-III and relapse (N=20), including covariates of age, mood, anxiety and motivation.

Results: The systematic review demonstrated substantial support for a deficit in emotional decision-making ability in alcohol-dependence. Methodological quality of the reviewed papers was moderate to high. Deficits in performance on a task of emotional decision-making compared to healthy controls indicated a reduced learning curve in alcohol dependent samples. Limitations of the studies included failure to report power analyses and effect sizes, insufficient detail regarding methodology and exclusion of common comorbidities in alcohol-dependence. The empirical study demonstrated clinically significant cognitive impairment in a sample of severely alcohol dependent individuals in the early stages following detoxification. In a smaller sample, cognitive functioning was not found to be predictive of relapse at one-month post-detoxification. Associations were identified between age and ACE-III score and between age and relapse status. Age was not predictive of outcome.

Conclusions: The available evidence points towards the existence of emotional decision-making deficits in alcohol dependent individuals. These are likely to impact on the ability of individuals make the health behaviour changes required to recover from alcohol dependence. Further research may be helpful in identifying factors associated with increased decision-making deficit in this specific population and investigating the processes underlying such difficulties. The clinical normative dataset presented in the empirical study points towards generalised cognitive impairment during the early stages of abstinence which may negatively impact on ability to engage meaningfully with psychosocial interventions. Performance on the ACE-III was not found to predict relapse in the current sample. Previous research would suggest that the links between cognitive functioning and relapse are less well defined in alcohol-misusing samples than in the wider substance-misuse population. Therefore future research may help to clarify this association in alcohol dependent samples. It is acknowledged that the ACE-III is yet to be validated for use in the

alcohol dependent population and is limited in its ability to assess executive functions.

Given the high prevalence of executive functioning deficits in the alcohol dependent population, it seems of importance to use cognitive screening tools which place appropriate emphasis on these abilities. Service providers are encouraged to incorporate routine cognitive screening into clinical practice and consider the implications of cognitive impairment at both individual and service delivery levels.

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CHAPTER 1. SYSTEMATIC LITERATURE REVIEW

Evidence for Impairment of Emotional Decision-Making Ability in Alcohol Dependence: A Systematic Review

(7367 words, excluding abstract and references)

Written in accordance with the author guidelines for submission to the journal *Drug and Alcohol Dependence*

(Author's Guidelines – see Appendix 1)

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1.1 ABSTRACT

Background: The evidence base for emotional decision-making deficits in alcohol dependency is well established. The aim of this review was to collate objective evidence from studies of decision-making using the Iowa Gambling Task (IGT) in alcohol dependent (AD) samples, to offer an indication of the methodological rigour of these studies, and to consider avenues for future research in this area.

Method: A comprehensive search strategy resulted in the systematic review of 18 studies investigating emotional decision-making ability in alcohol dependent populations. Quality ratings indicated the studies to be of moderate to high quality overall.

Results: Of 17 studies comparing AD samples to healthy controls, 12 reported poorer performance in the AD sample in overall IGT performance. Support was also found for a reduced level of improvement across the blocks of the task in AD participants. Evidence for factors influencing decision-making ability in this group was wide-ranging and demonstrated mixed results. History of conduct disorder and presence of antisocial personality traits may contribute to decision-making deficits in some AD individuals.

Conclusions: The available evidence points towards the existence of emotional decision-making deficits in AD individuals. The relevance of assessing this ability in alcohol dependence is discussed and the implications for clinical practice considered. Suggestions are made for future research.

Keywords: Alcohol Dependence, Emotional Decision-Making, Iowa Gambling Task

1.2 INTRODUCTION

Alcohol misuse and dependency are major health problems worldwide. It has been estimated that in 2004 3.8% of deaths were attributable to alcohol, with the highest proportion of these in the European region (Rehm et al. 2009). From an economic perspective, the costs to society in relation to loss of productivity, healthcare and law enforcement are vast (Rehm et al., 2009). The implications for an individual's social and occupational functioning are striking, as the compulsion to obtain alcohol persists despite negative consequences for the individual and those around them. It is this repeated pattern of apparently poor decision-making that forms one of the so-called 'hallmarks' of addiction, including alcohol-dependency (American Psychiatric Association, 1994). In a review of the literature, Sher et al. (2005) outlined a number of factors potentially involved in the etiology of alcohol use disorders; including the areas of epidemiology, genetics, personality, neuropsychology, parenting and social factors. One particular alcohol-related condition that remains poorly conceptualised is alcohol-related brain damage (ARBD).

1.2.1 *Alcohol-Related Brain Damage*

ARBD is a term used to describe functional and structural changes to the brain as a result of long-term consumption of alcohol at harmful levels (Cox et al., 2004). These changes are thought to be the result of a combination of factors, including toxicity of alcohol on the brain, nutritional deficiency, cerebrovascular disturbances and head injury (Kopelman et al., 2009; Thomson et al., 2012). ARBD itself is not a formal diagnosis, but deficits of this nature are considered to be subsumed within two related diagnoses in the ICD-10: Amnesic Syndrome due to alcohol (f10.6) and Alcohol related dementia (f10.73) (World Health Organisation, 1992). ARBD is a heterogeneous condition with a wide variety of presentations, however it is widely accepted that impairments in memory and executive

functioning are present in most people (Bates et al., 2002). Whilst alcohol has been demonstrated to affect numerous brain regions, and overall brain volume and integrity (for review see e.g. Rosenbloom & Pfefferbaum, 1995), one area that appears to be particularly vulnerable to the effects of alcohol is the frontal cortex (Ratti et al., 2002; Chanraud et al., 2007).

1.2.2 *Frontal lobes*

As a result of its complexity and links with almost all of the other components of the central nervous system (Moselhy et al., 2001), the frontal cortex is understood to serve as the neural substrate for a wide range of cognitive functions; often collectively termed as 'executive functions'. Research evidence indicates that the brains of alcohol dependent individuals are smaller than those of healthy non-alcoholics. For the most part, this shrinkage is believed to be the result of reduced white matter volume as opposed to loss of grey matter, or cortical tissue (Harper et al., 1985 and de la Monte, 1998; both cited in Harper, 1998). The frontal lobes in particular suffer from greater volume loss in comparison to other brain regions. In a review of alcohol-related brain damage, Harper (1998) suggested that this may be the result of the higher proportion of white matter compared to grey matter in this region. However decreases in grey matter have also been identified in the frontal lobes of alcohol dependent individuals by use of MRI (Chanraud et al., 2007). A number of researchers have investigated the basis for reduced brain volume. From a neurobiological perspective, many of the effects of alcohol on the brain are thought to be resultant of the effects of alcohol on various neurotransmitter systems, such as glutamate, aspartate, GABA, noradrenaline, dopamine and serotonin (De Witte et al., 2003). With repeated exposure to alcohol, these systems adapt accordingly to account for the chemical changes within the brain environment. As a result, during any period of withdrawal, the

concentrations of some of these neurotransmitters within the brain can increase, leading to toxicity and, ultimately, cell death (Weiss & Porrino, 2002).

1.2.3 *Executive functioning*

In his model of frontal lobe functioning, Stuss (2011) asserted that executive functioning constitutes 'higher order' functioning which serves to control and oversee more automatic cognitive functions. It is these processes that afford humans the ability to plan, organise and problem solve. Thus, whilst an individual may be able to effectively compensate for a deficit in a primary cognitive function if frontal lobe functioning is intact, deficits in more fluid abilities, such as the executive functions, are likely to result in widespread difficulties in day-to-day life (Lezak, 2004). In a review of frontal lobe functions, Moselhy et al. (2001) reported that despite preserved general cognitive functioning, people who misuse alcohol often demonstrate deficits in executive functioning (cognitive flexibility, problem solving, abstract reasoning, visuo-motor coordination, learning, conditioning, and memory) (pp. 362-363). Research would also suggest that whilst functioning, on the whole, has been shown to improve with abstinence, executive dysfunction appears to remain (e.g. Chanraud et al., 2007; Nakamura et al., 2014). Executive functioning deficits have long been associated with difficulties maintaining sobriety from alcohol and also poorer outcomes following treatment for substance misuse (Goldstein & Volkow, 2002 and Moselhy, 2001; respectively). It is therefore unsurprising that much research has focused on understanding the role of executive functioning in the development and maintenance of substance addiction. One facet of such abilities that has been particularly researched has been decision-making.

1.2.4 *Decision-Making Ability*

As mentioned, substance dependency is a disorder characterised by compromised decision-making processes (Jeste & Saks, 2006). In his model of frontal lobe functioning, Stuss (2011) made a distinction between four conceptually distinct components: task setting, task monitoring (both thought to rely largely on the dorsolateral prefrontal cortex), emotionally driven behavioural control involved in the recognition of rewards (ventromedial prefrontal cortex; VMPFC), and metacognition including goal-directed behaviour and self-awareness (frontal poles). From this perspective, deficits in decision-making could conceivably result from a breakdown of any combination of these sub-systems of executive functioning. In the context of addictions, where individuals may repeatedly make decisions in favour of immediate reward despite negative future consequences, the role of emotionally driven behavioural control seems of particular relevance. Therefore, for the purposes of the current review, the focus of discussion will be on decision-making which implicates such processes.

1.2.5 *The Iowa Gambling Task*

The Iowa Gambling Task (IGT; Bechara et al., 1994) is a widely-used, computerised, behavioural paradigm designed to assess decision making abilities, developed for use with patients with VMPFC lesions. It is an implicit gambling task; that is, one in which the contingencies of each choice are unknown to the participant and therefore decisions must be made under conditions of uncertainty. Participants are instructed to gain as much imaginary money as possible by making 100 selections from four decks of cards (A, B, C, D). With each card choice, the participant either gains or loses money. Each deck differs in the size of reward and penalty, but also in frequency of punishment. Of the four decks, A and B

are considered 'risky' or disadvantageous decks (high immediate gain followed by high penalty), choices from which will eventually lead to a net loss. C and D are considered advantageous and lead to an overall net gain (low immediate gain followed by low penalty) (Bechara, Tranel & Damasio, 2000). This schedule of reward vs penalty is unknown to the participant.

A number of outcome measures may be calculated from the IGT, including number of choices from each deck, number of advantageous choices, number of disadvantageous choices and monetary outcome. Within the literature to date, the most commonly used outcome is the net score, which is the number of cards selected from advantageous decks minus those from disadvantageous ones. Another common outcome measure is to look at performance across different stages of the task. Use of the total net score alone may overlook relevant patterns in performance and learning effects that may be evident as the participant's familiarity with the task increases. Given that alcohol use has been associated with neuropsychological deficits, including impairment of memory and aspects of new learning (Bates et al., 2002), this outcome measure is thought to be of particular relevance for the current review (see appendix 2 for further detail relating to measurement of outcome in the IGT). The IGT is thought to be ecologically valid and simulates real-life decision-making situations which typically involve elements of uncertainty, reward and punishment (Bechara et al., 1994; Bechara et al., 2000).

Findings from studies using the IGT in populations of people with VMPFC lesions highlighted a tendency for this group to persist in making disadvantageous choices, despite explicit feedback regarding the losses incurred (Bechara et al., 2000). This pattern of performance

has come to be termed ‘myopia for the future’ (Bechara et al., 2000, p298) and has also been demonstrated in studies of substance-misusing populations (e.g. Bechara & Damasio, 2002; Bechara et al., 2002). It has been suggested that this pattern of persistent disadvantageous decision-making in substance-dependent individuals (SDIs) is underpinned by deficits in emotional signalling systems in the brain. Originally described by Damasio (1994; cited in Verdejo-Garcia & Bechara, 2009), ‘somatic markers’ are an emotional mechanism associated with previous experience of situations that allow for anticipation of the outcome of a new, ambiguous situation. The somatic marker model of addiction proposes that, in SDIs, hyperactivity in the amygdala or ‘impulsive system’ may serve to increase the salience of immediate rewards; whilst underactivity in the prefrontal cortex or ‘reflective system’ reduces the ability to look forward to the future consequences of a given action (Verdejo-Garcia & Bechara, 2009). Therefore, in situations of ambiguity – as considered to be measured by the IGT – SDIs have reduced capacity to inhibit behaviours which will lead to immediate reward. As with other executive functions, evidence would suggest that impairment in decision-making ability may persist even following years of abstinence (e.g. Fein et al., 2004).

1.2.6 *Decision-Making Deficits in Alcohol Dependence*

The clinical relevance of characterising the nature of decision-making deficits in the alcohol dependent (AD) population is clear, considering that it may constitute a mechanism by which certain individuals are at increased risk of developing and maintaining substance use problems (Miranda et al., 2009). With a more sophisticated understanding of these deficits, policy, assessment and care planning for this group may be able to be tailored to their specific profile of strengths and weaknesses. Clinicians are often asked to comment on the capacity of patients with alcohol-use disorders to make reasoned judgements regarding

their welfare and finances (Hazelton et al., 2003). As has been highlighted, this is one particular area where this population may be at a distinct disadvantage; although preserved functioning in other cognitive domains (e.g. 'functional reorganization' hypothesis posited by Pfefferbaum et al., 2001), personality traits or coping styles (Ando et al., 2012) may serve to conceal or compensate for such difficulties. From a treatment perspective, evidence suggests a link between better decision-making ability and increased motivation to change drinking behaviour at treatment entry (Le Berre et al., 2012). In addition, concerns regarding response to treatment were highlighted by Tomassini et al. (2012), who further raised the possibility that decision-making deficits in this population may lead to increased interpersonal difficulties and risk of harm to self or others. With the potential for such wide-ranging implications, increased understanding of deficits in decision-making in alcohol-dependence is of great importance and may impact on the emphasis given to assessing 'hot' decision-making abilities (Brand et al., 2007), as are engaged in ambiguous situations.

Brevers et al. (2014) make reference to the relative wealth of research into poor decision-making under conditions of ambiguity in alcohol dependence as a rationale for expanding the evidence-base for the related concept of risky decision-making. It therefore seems prudent to assimilate the findings in relation to this particular area. Zorlu et al. (2013a) highlight a number of methodological challenges in interpreting the findings of such research owing to the high degree of poly-substance misuse and other comorbidities in the experimental samples. Arguably, inclusion of such groups is reflective of the presentations of most AD populations. However their inclusion leads to difficulties interpreting any findings. Furthermore, polysubstance abuse has been reported to result in poorer

performance on the IGT compared to abuse of any individual substance (Grant et al., 2000; Rotheram-Fuller, 2004). In relation to comorbidity, there is a large amount of research which points toward decision-making deficits across a number of psychiatric and medical conditions (for a summary, see Buelow & Suhr, 2009). Therefore, it seems of relevance to try to summarise the findings in relation to emotional decision-making ability in as 'pure' an AD population as possible to try to establish the relative contributions of this particular disorder – or pre-existing impairments in people who go on to develop alcohol-dependence – to the impairments described in the literature.

In a review of behavioural decision-making and neuroimaging studies, Dom et al. (2005) described consistent decision-making impairment in patients with substance-use disorders (SUDs) across eleven studies which focused on behavioural decision-making paradigms. Ten of these studies used the IGT. Whilst this review provided substantial evidence in support of impaired decision-making in SUDs, the findings must be interpreted in light of the following limitations. Firstly, the review included a wide variety of substance misuse samples (amphetamines, opiates, poly-drug misuse, alcohol, methadone, 'substance use disorder', and 'substance dependency') and one VMPFC lesion sample. The severity of dependency for most of these groups was not clear, nor was the presence of comorbid use of other substances in addition to the main substance of misuse. This variation in samples makes the assimilation of findings somewhat difficult, limiting the ability to generalise to any given substance-misuse population. Furthermore, the study characteristics would suggest that the samples varied in their duration of abstinence and ongoing use of prescribed maintenance substances, which may have influenced decision-making ability. Finally, the review only reported the findings from one study of AD participants. In light of

the range of evidence to suggest that AD individuals are impaired in tasks of emotional decision-making ability and to build on the findings from the aforementioned review, the aim of the current systematic review was to describe and evaluate the evidence for an objective deficit in emotional decision-making ability in adults with alcohol-dependency.

1.3 METHOD

1.3.1 *Literature search strategy*

The electronic literature search was conducted in June/July 2014. It was not feasible to translate texts from other languages, therefore searches were limited to studies published in English. Other limits included human-only studies and studies of adult participants (18+yrs). The Cochrane Database of Abstracts of Reviews of Effects (DARE) was consulted to ensure that a similar review had not recently been conducted.

Four electronic databases were searched, from the disciplines of health and psychology: PsycINFO (1987 to June week 4 2014), EMBASE (1980 to 2014 week 26), OvidMEDLINE(R) (1946 to June week 3 2013) and CINAHL Plus. Searches were performed using default 'multi-purpose' fields and included title, abstract, subject heading and keyword. For all databases, the following keyword search was employed: [alcoholi* OR alcohol* adj3 depend* OR alcohol* adj3 addict* OR alcohol* adj3 abus*] AND [decisi* adj mak* OR ventromedial prefrontal cortex OR gambl* adj3 task*].

Two journals which regularly publish on cognitive impairment in relation to substance misuse were hand-searched online for relevant papers since 2004: 'Alcoholism: Clinical and

Experimental Research (Vol. 28, issue 1 to Vol. 38, issue 7)' and 'Alcohol and Alcoholism (Vol. 39, issue 1 to Vol. 49, issue 4)'. Reference lists of the studies included in the current review were also searched for relevant papers.

1.3.2 *Data collection and analysis*

References were selected by the main author using an iterative approach, involving a number of 'screens' of the data. With each screen, the inclusion and exclusion criteria were systematically applied and items removed according to these (as detailed in Table 1). Following an initial removal of duplicates, articles were screened for suitability by title and abstract. The remaining 71 articles were reviewed in full, resulting in the exclusion of 53 studies (see Appendix 3 for details and reasons for exclusion). The remaining 18 studies were included in the current review. See Figure 1 for an outline of the search results and selection process.

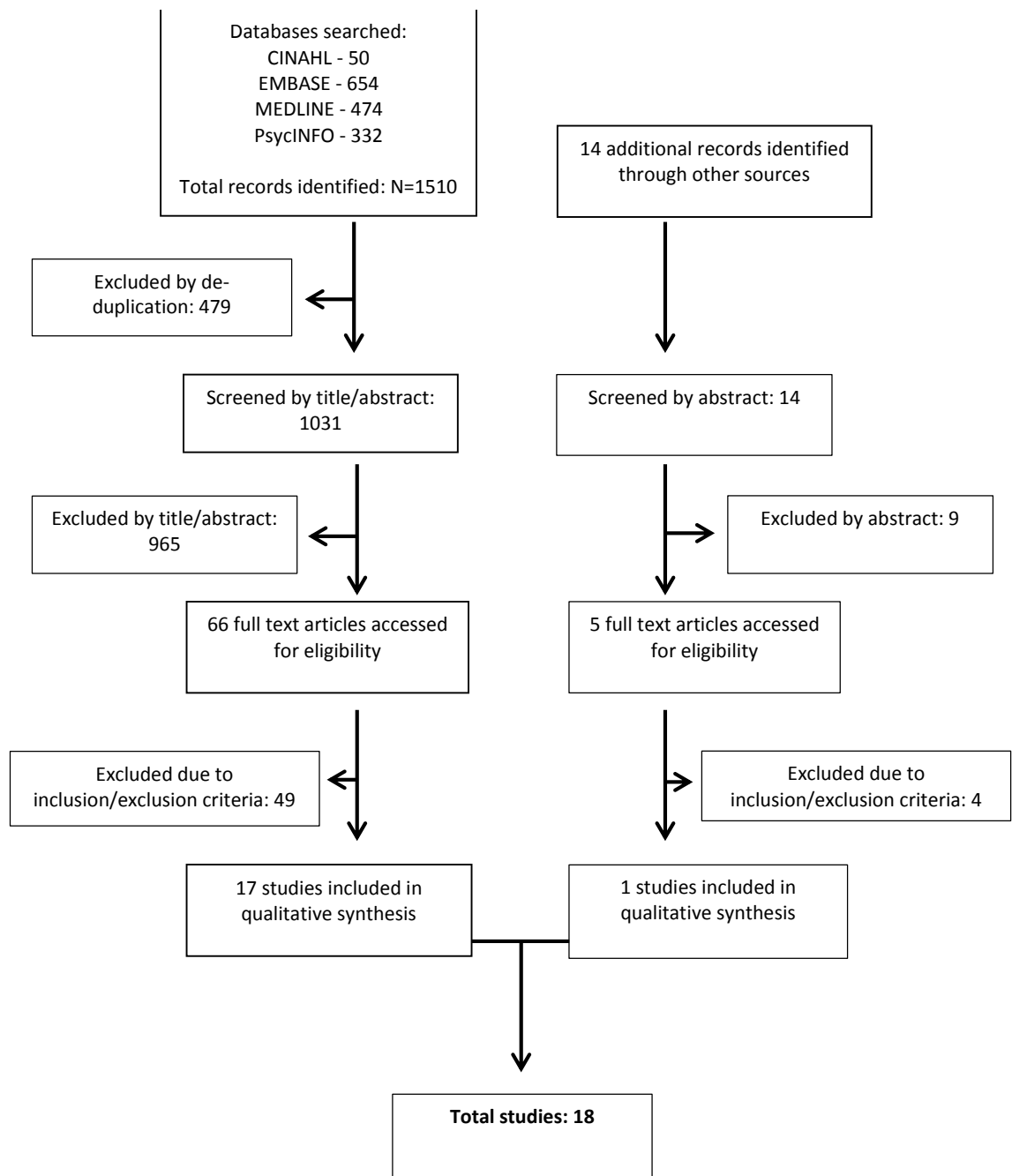
Table 1- Inclusion and Exclusion Criteria for studies

Inclusion Criteria
<ol style="list-style-type: none"> 1. Primary empirical papers reporting on quantitative data 2. Studies that examined populations of adults aged 18-65yrs 3. Studies that examined participants meeting recognised criteria for alcohol dependence 4. Studies which used the Iowa Gambling Task (IGT) as a measure of emotional decision-making ability 5. Studies which measured decision-making in terms of risky performance
Exclusion Criteria
<ol style="list-style-type: none"> 1. Studies not published in English 2. Case studies, unpublished dissertations, or review articles 3. Articles which were not peer reviewed 4. Studies which measured performance on the IGT in terms of reaction time or biological/physiological outcomes 5. Studies where participants are known have a significant history of or current dependence to other drugs (i.e. meet diagnostic criteria for two or more substances), or where this has not been explicitly reported

1.3.3 *Assessment of Methodological Quality*

A checklist was devised, informed by the aims of the review, to assess the methodological quality of each included study. The final checklist items were based on the SIGN (Scottish Intercollegiate Guidelines Network) 50 Methodology Checklist 4 for case control studies (SIGN, 2011; pp67-72) and CONSORT guidelines (2010). Using the checklist, each paper could score a maximum of 19 points (see Appendix 4). Each paper was rated initially by the lead author. The papers were then rated by a second author and Cohen's kappa statistic indicated substantial agreement between the raters, Kappa=.806 (95% CI, .741 to .871). Discrepancies were resolved through discussion. Based on arbitrary cut-offs, studies were rated high, moderate or low quality (high – 80%+; moderate – 50-79%; low – <50%).

Figure 1 - Search Results and Selection Process



Flow diagram adapted from: Moher et al. (The PRISMA Group, 2009).

1.4 RESULTS

1.4.1 *Study Characteristics*

Study demographic information, quality ratings and key outcomes relating to the IGT are presented in Table 2. Studies differed by country of origin and therefore utilised various translations of the original IGT. Most articles reported modest sample sizes, with number of AD participants ranging from 17 (Zorlu et al., 2013b) to 58 (Fein et al., 2006). Most studies were mixed-gender, with 5 including only men. Duration of abstinence at the time of testing ranged from 0 days (active drinkers; Fein et al., 2006) to over six years (Ando et al., 2012; Fein et al., 2004). Seventeen of the reviewed articles adopted a case-control design, comparing AD samples to non-alcohol dependent healthy controls (HC). Ando et al. (2012) was the only study not to include a control group; instead comparing a sample of ADs in short-term abstinence (mean 12 weeks) to those in longer-term abstinence (mean 327 weeks).

1.4.2 *Methodological Review*

Only two studies achieved high quality assessment ratings (Cordovil et al., 2010 and Miranda et al., 2009), with the majority (n=15) rated moderate. Only one met less than 50% of the quality criteria assessed (Kim et al., 2006). A number of studies lost marks in relation to insufficient information to rate the item as positive; this was the case especially for items related to recruitment, exclusion criteria, comparability of control groups with experimental groups and description of methodology. It is therefore difficult to comment on a number of potential sources of bias in these areas. However, it is possible that these items are reflective of poor reporting quality rather than methodological weaknesses. Final quality ratings for each paper can be seen in Appendix 5.

1.4.3 Narrative Review

The following comprises a narrative review of findings derived from the search strategy outlined in Figure 1. Only findings related to the IGT are reported. The results will be presented in two sections. Firstly, findings in relation to IGT performance in alcohol dependent subjects compared to healthy controls will be described. Secondly, findings in relation to IGT performance between subgroups of AD samples will be presented. Any additional findings which have examined other variables in relation to IGT performance in alcohol dependent samples will be summarised in this section.

1.4.3.1 IGT Performance – Alcohol Dependent (AD) versus Healthy Controls (HC)

Of the 17 studies which included a control group, 12 (70.59%) reported significantly poorer overall IGT performance in the alcohol dependent sample compared to controls (Brevers et al., 2014; Cordovil et al., 2010; Fein et al., 2004; Goudriaan et al., 2005; Kim et al., 2006; Kim et al., 2011; Le Berre et al., 2014; Miranda et al., 2009; Noel et al., 2007; Noel et al., 2011; Salgado et al., 2009; Tomassini et al., 2012). Thirteen papers commented on performance by block or stage of the task, with 11 (84.61%) reporting poorer performance in AD samples compared to controls on one or more of the five blocks of the IGT (Brevers et al., 2014; Cordovil et al., 2010; Kim et al., 2006; Kim et al., 2011; Le Berre et al., 2014; Miranda et al., 2009; Noel et al., 2007; Noel et al., 2011; Salgado et al., 2009; Tomassini et al., 2012; Zorlu et al., 2013b). Two identified no group by block differences (Goudriaan et al., 2005; Loeber et al., 2009). Healthy controls were found to perform better than AD participants in block two in two studies (Salgado et al., 2009; Tomassini et al., 2012), block three in three studies (Kim et al., 2006; Kim et al., 2011; Miranda et al., 2009), block four in six studies (Cordovil et al., 2010; Kim et al., 2006; Kim et al., 2011; Salgado et al., 2009; Tomassini et al., 2012; Zorlu et al., 2013b) and block five in nine studies (Kim et al., 2006;

Table 2- Study Demographic Information, Quality Ratings and Key Outcomes

Study, country and quality rating	Population and sample Size (n =)	Groups matched for:	Average Abstinence Duration: mean(sd)	IGT Total/Overall Performance: difference observed? (yes/no) <i>d</i> = Cohen's <i>d</i> (where reported or able to be calculated)	IGT Performance by block Difference observed? (yes/no)
Ando et al. (2012) Hungary 10/19	AD: Long-term abstinence (LTA) – 45 Short-term abstinence (STA) – 43	Gender IQ Years of education AD severity Nicotine dependence	LTA – 327.82weeks(165.57) STA – 12.70weeks(6.92)	No (STA vs LTA) Both groups consistently performed at chance level. There was no significant difference between groups.	Yes (both STA and LTA) No learning effect observed for either group
Bowden-Jones et al. (2005) UK 10/19	AD – 21 HC – 20		21days	No (AD vs HC) Yes (relapsed AD vs abstinent AD)	Not reported
Brevers et al. (2014) Belgium 12/19	AD: 30 HC: 30	Age Years of education Gender	22.07days(3.49)	Yes (AD vs HC) AD made significantly more disadvantageous decisions overall	Yes (AD vs HC) AD showed no improvement across blocks whilst HC did Significantly poorer choices on blocks 3, 4 and 5.
Cordovil et al. (2010) Belgium 16/19	AD – 35 (split into two for the analysis of IGT outcomes) HC – 22	Age Gender Educational level	Time point 1 – 0-1days Time point 2 – 14-18days	Yes (AD vs HC) AD made more disadvantageous choices: - <i>d</i> (t1) vs HC = 0.71 - <i>d</i> (t2) vs HC = 1.01 and accrued lower net scores compared to controls: - <i>d</i> (t1) vs HC = -0.69 - <i>d</i> (t2) vs HC = -0.96 No (recently abstinent AD vs longer abstinent AD) - <i>d</i> (t1) vs (t2) = -0.22	Yes (AD vs HC) Only significant difference between AD and controls at block 4 (controls scored higher): - <i>d</i> (t1 and t2) compared to HC = > 0.66 No (AD t1 vs AD t2)
Fein et al. (2004) USA	AD – 43 HC – 58	Age Years of education	AD – Males: 6.79yrs Females: 7.13yrs	Yes (AD vs HC) AD group performed significantly worse compared to controls:	Not reported

Study, country and quality rating	Population and sample Size (n =)	Groups matched for:	Average Abstinence Duration: mean(sd)	IGT Total/Overall Performance: difference observed? (yes/no) <i>d</i> = Cohen's <i>d</i> (where reported or able to be calculated)	IGT Performance by block Difference observed? (yes/no)
15/19			(Minimum 6 months)	- <i>d</i> = -0.52 (calculated using data published in Fein <i>et al.</i> , 2006)	
Fein et al. (2006) USA 15/19	AD (Treatment naïve) – 58 HC – 58	Age Gender	Actively drinking	No (AD vs HC) - <i>d</i> (AD vs HC) = -0.16 No (Tx naïve AD vs abstinent AD) - <i>d</i> (TxN AD vs Abst) = 0.33	Not reported
Goudriaan et al. (2005) The Netherlands 13/19	AD – 46 HC – 49	Gender IQ	3-12months	Yes (AD vs HC) AD chose less cards from the advantageous decks compared to controls: - <i>d</i> = 0.67	No (AD vs HC) AD performance did improve across trials but AD selected 'good' decks less frequently than controls. No interaction between group and block was present between AD and HC.
Kim et al. (2006) South Korea 9/19	AD – 56 (28 with history of CD, 28 without) HC – 40 (10 with history of CD, 30 without)	Age Gender (all male)	Minimum 2 weeks	Original IGT Yes (AD CD- and AD CD+ vs HC CD-) No (AD CD- and AD CD+ vs HC CD+) AD patients as a whole showed impaired DM compared to HC CD- but not compared to HC CD+ No (AD CD- vs AD CD+) No difference was observed between AD CD- and AD CD+. Variant IGT No (AD vs HC or AD CD+ vs AD CD-)	Original IGT Block 3 Yes (AD CD+ and HC CD+ vs HC CD-) No (AD CD- vs HC CD-) HC CD+ and AD CD+ (but not AD CD-) performed worse than HC CD- in block 3 Blocks 4 & 5 Yes (whole AD sample and HC CD+ vs HC CD-) AD CD+, AD CD- and HC CD+ performed worse than HC CD- in blocks 4 and 5 Variant IGT

Study, country and quality rating	Population and sample Size (n =)	Groups matched for:	Average Abstinence Duration: mean(sd)	IGT Total/Overall Performance: difference observed? (yes/no) <i>d</i> = Cohen's <i>d</i> (where reported or able to be calculated)	IGT Performance by block Difference observed? (yes/no)
					No No group differences existed but overall improvements were seen across the whole sample as task progressed. No group by block interaction was observed.
Kim et al. (2011) South Korea 14/19	AD – 23 HC – 21	Age Gender (all male) IQ	2 weeks	Yes (AD vs HC) AD patients performed poorly on IGT compared to HC: <i>d</i> = 1.27 <i>d</i> (deckA) = 0.74 <i>d</i> (deckB) = 0.93 <i>d</i> (deckC) = -0.73 <i>d</i> (deckD) = -0.94	Yes (AD vs HC) AD demonstrated impaired DM on the IGT compared to HC on blocks 3-5
Le Berre et al. (2014) France 13/19	AD – 30 HC(DM) – 45 HC(imag) - 27	Age Level of education Gender	Average – 12.63(7.08)days (range 7-40)	Yes (AD vs HC) ADs selected more high-risk cards than controls. <i>d</i> (total IGT)= 0.52 <i>d</i> (deckA) = -0.24 <i>d</i> (deckB) = 1.26 <i>d</i> (deckC) = -1.06 <i>d</i> (deckD) = 0.09	Yes (AD vs HC) AD made significantly poorer choices in block 5 compared to HC
Loeber et al. (2009) Germany 12/19	AD – 48 (AD Lo Detox – 27; AD Hi Detox – 21) HC – 36	Age Gender Premorbid IQ	Average – 15.65days(6.69); range – 4-37	No (AD vs HC) No difference was observed on overall IGT performance between whole AD sample and controls Yes (Hi Detox vs Lo Detox)	No (AD vs HC) Both groups (AD and HC) showed a similar degree of improvement across blocks Yes (Hi Detox vs Lo Detox)

Study, country and quality rating	Population and sample Size (n =)	Groups matched for:	Average Abstinence Duration: mean(sd)	IGT Total/Overall Performance: difference observed? (yes/no) <i>d</i> = Cohen's <i>d</i> (where reported or able to be calculated)	IGT Performance by block Difference observed? (yes/no)
				Hi Detox demonstrated poorer overall IGT performance compared to Lo Detox Yes (recently abstinent vs longer abstinent; post hoc analysis)	Lo detox demonstrated a greater increase in advantageous choices across blocks compared to Hi Detox
Miranda et al. (2009) USA 16/19	AD – 22 AD + ASPD – 17 HC – 21		AD – 13.64months(21.34) AD + ASPD – 13.56(21.65) HC – 10.2(19.83)	Yes (AD and AD+ASPD vs HC) Overall AD and AD + ASPD groups performed worse than HC. No (AD vs AD+ASPD)	Yes (AD vs HC) AD performed worse than HC at block 3 Yes (AD+ASPD vs AD and HC) AD + ASPD performed worse than both controls and AD at block 5.
Noel et al. (2007) Belgium 12/19	AD – 30 HC – 30	Age Gender Education level	AD – 19.3days(2.5) (minimum 15days) HC – 2.1(1.4)	Yes (AD vs HC) AD performed worse than controls by selecting more cards from disadvantageous decks.	Yes (AD vs HC) AD performed significantly worse in block 5 of the IGT
Noel et al. (2011) Belgium 12/19	AD – 30 HC – 30	Age Gender Education level	AD – 19.3(2.5) HC – 2.1(1.4)	Yes (AD vs HC)	Yes (AD vs HC) HC performed significantly better on the IGT at stage 5.
Salgado et al. (2009) Brazil 15/19	AD – 31 HC – 30	Age Gender Years of education IQ	15-120days (split into short-term and long term abstinence for comparison; 15-30days and 60-120days, respectively)	Yes (AD vs HC) No (AD short-term vs AD long-term abstinence)	Yes (AD vs HC) HC performed significantly better on the IGT at blocks 2, 4 and 5

Study, country and quality rating	Population and sample Size (n =)	Groups matched for:	Average Abstinence Duration: mean(sd)	IGT Total/Overall Performance: difference observed? (yes/no)	IGT Performance by block
				<i>d</i> = Cohen's <i>d</i> (where reported or able to be calculated)	Difference observed? (yes/no)
Tomassini et al. (2012) Italy 11/19	AD – 27 HC – 24	Age Gender	AD – 16.85months (13.21), minimum 6months	Yes (AD vs HC)	Yes (AD vs HC) HC performed significantly better in blocks 2, 4 and 5. Both groups demonstrated improvement over time, HC demonstrated more than AD.
Zorlu et al. (2013a) Turkey 13/19	AD – 30 HC – 30	Age Gender Level of Education	AD were recruited between days 20-30 of inpatient treatment	No (AD vs HC)	Not reported
Zorlu et al. (2013b) Turkey 14/19	AD – 17 HC – 16	Age Years of education	AD – 17.1 +/- 1.8days	No (AD vs HC)	Yes (AD vs HC) HC shifted their choices from disadvantageous to advantageous, particularly over the last two blocks whilst AD did not. AD performance was significantly poorer than HC in block 5.

Kim et al., 2011; Le Berre et al., 2014; Miranda et al., 2009; Noel et al., 2007; Noel et al., 2011; Salgado et al., 2009; Tomassini et al., 2012; Zorlu et al., 2013b).

As can be seen in Table 2, three of the studies which split their AD samples into subgroups analysed overall IGT performance in ADs without commenting on subgroup comparisons with controls (Bowden-Jones et al., 2005; Loeber et al., 2009; Salgado et al., 2009).

One study investigated the influence of a history of conduct disorder (CD) on IGT performance in a group of AD participants and controls both with and without a history of CD (Kim et al., 2006). Net scores on the original IGT were found to be significantly lower in both AD samples compared to healthy controls without conduct disorder but not those with. There were no group differences observed on the variant IGT. In the original IGT, significant differences in performance were identified in blocks three, four and five. In block three, healthy controls without a history of CD chose more advantageously than AD participants with a history of CD, but not ADs without. In blocks four and five, healthy controls without a history of CD chose more advantageously than all other groups. In the variant IGT, a significant effect of block was found across the whole sample. No effect of group or group by block interaction was found, indicating that all groups demonstrated a similar rate of improvement in performance.

In a study investigating the impact of antisocial personality disorder (ASPD) on decision-making, the DM ability of thirty nine male AD participants was compared to that of 21 male controls (Miranda et al., 2009). The AD group was split into those meeting diagnostic

criteria for antisocial personality disorder (ASPD) and those who did not. Both AD groups were found to independently perform significantly worse than controls in the IGT (sum of net scores across all five blocks). In block three, the AD group without ASPD performed significantly worse than the control group, with no other differences reported for this block. In block five, the AD+ASPD group performed significantly worse than controls. No such difference was identified between AD without ASPD and controls. No group differences were identified for any other blocks.

In addition to comparing performance on the IGT, two studies sought to assess participants' explicit knowledge of which decks were risky and which were advantageous, demonstrating opposing findings. Goudriaan et al. (2005) assessed this at the end of the entire task and established that AD participants identified fewer decks correctly than controls. Miranda et al. (2009) assessed insight at the end of each of the five blocks and asserted that by the end of the task, there was no difference between AD participants and controls.

1.4.3.2 IGT Performance – AD Subgroup Comparisons and Other Associations

A number of studies compared subgroups of AD participants on their decision-making ability using the IGT, demonstrating a variety of findings. Attempts were also made to investigate relationships between other variables in AD samples and decision-making ability. The following sections will summarise findings in relation to these. In cases where it was not clear if the sample used in the analysis was just AD or included the whole sample, findings are not reported.

Duration of Abstinence

Nine studies (50%) investigated different stages of abstinence in relation to IGT performance. Four included abstinence duration as a comparison in their main analysis, three of which found no significant difference in IGT performance between groups (Ando et al., 2012; Cordovil et al., 2010; Fein et al., 2006). The groups compared in these studies were average 12 weeks abstinence versus approximately six years, 0-1 days versus 14-18 days, and 0 days versus average 6-7 years, respectively. In contrast with these findings, Loeber et al. (2009) compared performance in those who had maintained abstinence for less than 16 days with those who had remained abstinent for 16 or more and reported that recently abstinent patients accrued a significantly lower overall net outcome on the IGT compared to longer abstinent patients. Four studies investigated correlations between duration of abstinence and IGT performance (Fein et al., 2004; Le Berre et al., 2014; Salgado et al., 2009; Tomassini et al., 2012). None reported a significant association between these two variables. Bowden-Jones et al. (2005) retrospectively compared the IGT scores at 21 days abstinence of AD participants who went on to relapse at three months versus those who remained abstinent. It was found that those who relapsed performed significantly worse overall on the IGT at the start of treatment than those who had remained abstinent.

Other Alcohol use related variables

Nine of the reviewed studies (50%) assessed other alcohol use-related variables and their association with IGT performance. Only one of these studies reported a significant association: Fein et al. (2004) found significant negative correlations between decision-making ability and both duration of alcohol use and duration of peak use. However, only duration of peak use remained significant after controlling for the effects of age in the

sample. Duration of peak use was also examined in Fein et al. (2006), who found no association with IGT performance in their AD sample. Similar constructs were examined by Ando et al. (2012), Kim et al. (2006), Le Berre et al. (2014) and Zorlu et al. (2013a); all of whom reported no significant association with IGT performance. As can be seen in Table 2, a variety of other alcohol use-related variables were also considered in association with decision-making ability in the AD samples. None of these demonstrated significant associations.

Personality, Temperament and mood

Six studies explicitly reported associations between personality traits/temperament and IGT performance in AD participants. Correlations with scores on measures of socialisation and externalisation with IGT performance highlighted no significant association in one long-term abstinent AD sample (Fein et al., 2004). Another study reported a significant association between ASPD diagnostic status and performance on the last three blocks of the IGT (Miranda et al., 2009). Further investigation of the sub-facets of ASPD failed to reveal associations between decision-making and degree of psychopathic traits but identified a significant inverse relationship between degree of anti-social personality traits with blocks three, four and five of the IGT. In a combined predictive model, they found the latter to mediate the difference in IGT performance between AD with ASPD and those without. In a study comparing AD participants with and without a history of conduct disorder, no difference in net IGT (original version and variant) or score across the final two blocks was observed between AD groups (Kim et al., 2006). Novelty seeking and self-reported tendency toward impulsivity have been negatively correlated with IGT performance (Noel et al., 2011 and Tomassini et al., 2012 respectively). Non-planning

impulsivity (or acting without forethought) was found to be associated with overall IGT performance and both non-planning and overall impulsivity (combining attentional, motor and non-planning) associated with block four, specifically. No association was identified between decision-making ability and depression (Loeber et al., 2009).

Neuropsychological and Executive Functioning

In relation to neuropsychological functioning, findings were mixed. Working memory was found to be positively correlated to IGT performance in one study (Fein et al., 2006) but no such association was found in another (Brevers et al., 2014). Similarly, set-shifting and perseveration were not found to be correlated with IGT performance in one study (Salgado et al., 2009) but Fein and colleagues (2006) identified a positive association between cognitive flexibility and decision-making. No correlations with IGT performance were found with dual tasking (Brevers et al., 2014) or motor impulsivity (Salgado et al., 2009). Number of categories produced in the Wisconsin Card Sorting Test was positively associated specifically with both block two and overall performance on the IGT in one study, whilst total errors and perseverative errors in the same task was negatively correlated with block two of the IGT (Kim et al., 2011). The same study identified a negative correlation between risky decision-making on the Game of Dice Task (a measure of explicit decision-making) and IGT block five. Response inhibition deficit was noted to predict impaired performance on the second half of the IGT in AD participants who achieved a net score of less than ten on the IGT (the best score of patients with VMPFC damage reported in Bechara et al., 2001) in one study (Noel et al., 2007). Considering other aspects of neuropsychological functioning, positive correlations were found between IGT performance and both delayed memory and spatial processing (Fein et al., 2006).

Brain Functioning and Integrity

Grey matter shrinkage, particularly in areas associated with decision-making, was found to be associated with poorer performance in the IGT (Le Berre et al., 2014). White matter integrity in the corpus callosum and left posterior cingulum was positively correlated with IGT performance in block 5 in another study, whilst no correlations were found between overall IGT performance and white matter integrity in any region for AD participants, despite various associations across the whole sample (Zorlu et al., 2013b).

1.5 DISCUSSION

1.5.1 Summary of Findings

This systematic review investigated decision-making deficits in alcohol dependent individuals. Using a structured search strategy, 18 studies reporting decision-making ability using the IGT in an alcohol dependent population were identified. The majority of these (12 of 17 eligible papers) identified a significant deficit in emotional decision-making in AD compared to controls across the entirety of the task. A majority also noted increased impairment compared to healthy controls as the task progressed (block 2 in two studies; block 3 in three studies; block 4 in six studies; block 5 in nine studies).

Two studies compared subgroups of AD individuals to control participants in their main analysis; indicating that history of conduct disorder may adversely impact on decision-making ability in both AD participants and controls and that comorbid ASPD may affect alcohol dependent individuals' decision-making in the late stages of the IGT. A variety of

other associations yielded mixed findings. Socialisation and externalisation revealed no significant association with IGT performance whilst self-reported impulsivity and novelty seeking were negatively correlated. One study revealed no association between depression and IGT performance. Duration of abstinence was not generally found to be related to IGT performance (seven of nine studies reported no significant findings), and findings were similar for other alcohol use-related variables (one of nine studies found a significant association – duration of peak alcohol use – however, another study found no such association). Investigations of neuropsychological findings demonstrated conflicting findings regarding associations between IGT performance and both working memory and cognitive flexibility. No correlations were found for dual-tasking or motor impulsivity and IGT performance. Some aspects of executive functioning (generation of categories, perseveration, explicit decision-making ability and response inhibition deficit) have been associated with poorer performance on the IGT as were delayed memory and spatial processing.

1.5.2 *Context of Findings: Methodological Limitations*

A number of methodological factors may have influenced the results obtained in the studies reviewed. No studies reported a priori sample size calculations or confidence intervals for findings in relation to IGT performance. Whilst many reported statistically significant results, without an indication of the power of the analysis it is possible that those reporting non-significant findings were underpowered to detect any difference between experimental groups. This seems particularly pertinent in the case of non-significant findings between subgroups of AD participants where differences may be more subtle and samples were often sub-groups of the larger group recruited. However, in the case of overall IGT performance compared to HC, sample sizes were comparable in those studies

that identified significant differences and those that did not. Had studies reported confidence intervals, it may have been possible to discern the degree of precision of the non-significant findings. In such instances where differences fail to meet statistical significance, differences that may be of clinical importance may fall within the bounds of confidence estimated. In the case of the current review, the risks of inadvertently accepting the null hypothesis are unlikely to result in any immediate harm. However, missing potentially clinically relevant information would seem to undermine the vast amount of research that has gone into this area to date.

Another item that was poorly reported was effect size. It was however possible to calculate this in studies which provided sufficient information. Using Cohen's conventional criteria for classifying size of effect (Cohen, 1992), the effect sizes obtained would suggest medium-high effect sizes in comparisons between AD groups and controls (see Table 2). Effect sizes for comparisons of AD subgroups tended to be smaller, supporting the hypothesis that differences between AD subgroups may be more subtle.

One area that seems of particular relevance when interpreting the current results is the degree of confound. In only 50% of papers was it deemed clear that exclusion criteria were the same for both cases and controls (with the obvious exception of the inclusion of alcohol-dependence/misuse for control groups). Alongside this, over a quarter of the papers provided insufficient detail to allow for a meaningful judgement of the comparability of the two groups. As can be seen in Table 2, controls were matched to AD groups on a number of variables; most commonly age (15 studies), education level (15 studies) and gender (14 studies). Only five however, reported matching groups on IQ level.

Although intuitively it seems reasonable to suggest that measures of IQ and measures of decision-making may be associated, a recent literature review indicated that variance in performance on the IGT was not, in fact, explained by performance in tasks of executive functioning and general cognitive ability (Toplak et al., 2010). The authors suggest that decision-making ability may therefore be conceptually separate to these other processes. Consistent with this review, findings in relation to cognitive functioning and decision-making in the current sample were variable, suggesting that these abilities may represent distinct processes in the alcohol dependent population also. Therefore failing to match groups on cognitive ability should not necessarily be viewed as a weakness.

Only half of the reviewed papers provided sufficient detail about the method to allow for replication. In particular, a number failed to comment on the order of test administration or randomisation procedures. It is acknowledged that the effects of fatigue can impact negatively on people's performance on standardised cognitive assessments (Lezak, 2004). Therefore, methods to control for such effects would be advisable in any study involving assessment of cognitive functioning, including decision-making.

A number of studies excluded participants on the basis of current or previous Axis I mental health disorders (15 studies), Axis II disorders (two studies), traumatic or organic brain injury (15 studies) and significant physical health problems (13 studies). Whilst such exclusionary criteria are likely to reduce confounding factors and aid in the attribution of any findings to alcohol-dependence, such comorbidities are common in alcohol dependent populations (e.g. Morgenstern et al., 1997 and Swendsen et al., 1998). Furthermore, it is noted from studies in the current review that have included comorbid populations (e.g. Kim

et al., 2006 and Miranda et al., 2009), that the decision-making deficits in the AD population may be mediated by comorbid mental health conditions. Therefore, to exclude participants on these grounds substantially reduces the generalisability of findings to the wider alcohol dependent population.

1.5.3 *Limitations of Review*

Owing to resource constraints, only papers published in English were included in this review. This limits the scope of research accessed and influences any findings in favour of Western societies. As the search was limited prior to reviewing, it is not possible to comment on how many non-English articles were excluded. As with any review, the selection process is likely to have incorporated a degree of selection bias. This may have been increased by the development of a unique quality rating measure. The degree of inter-rater reliability however was good, suggesting that at least in the interpretation of items assessed, variability was minimal. All of the studies in this review were of a case-control design. The observational nature of such designs relies on adequate control of confounding variables. As noted, it is difficult to know how well this was achieved in the reviewed studies. Such designs also lend themselves to potential spurious claims of causation. The IGT manual warns against inferring substance misuse-related frontal lobe damage when using the measure in substance-dependent populations (Bechara, 2007 cited in Buelow and Suhr, 2009). It is not possible from this type of study to tell the temporal sequence between, in this instance, alcohol-dependence and decision-making deficit.

Another potential limitation of this review was to restrict to studies of only the IGT. Unlike other implicit measures of decision-making (e.g. the Balloon Analogue Risk Task; Lejuez et

al., 2002) the IGT is considered to potentially measure two different types of decision-making: decision making under ambiguity and decision-making under risk. It was considered that this may allow for more sophisticated understanding of decision-making deficits as they present in this population. The incidence in some studies of reporting only overall or 'net' outcomes for the total IGT may reduce the construct validity of the measure (Buelow and Suhr, 2009). The studies reviewed here utilised this outcome measure either in isolation or alongside block or stage comparisons and therefore the findings using the former must be considered with this caveat.

Finally, it could be argued that a number of the items on this measure relate more to reporting quality than methodological quality (items 1, 3, 4, 9, 11, 14-19). Subsequently, some studies are likely to have been marked up or down for issues that do not necessarily reflect the ability of the study to address the review question. The rationale for including these items was largely owing to recognition that the reader can often only assess the methodological rigour of empirical studies based on the information provided in the article. Therefore, to effectively and critically appraise research articles, consistency and transparency of reporting is of great importance (see www.consort-statement.org). A published review of quality assessment systems echoed the importance of good reporting of evidence in empirical research and highlighted what the author deemed to be 'critical' items to be included in rating tools (Lohr, 2004). The ratings used in the current review reflect the relevant items in this publication. However, it is acknowledged that mere omission of information does not necessarily equate to methodological weakness. The items for the current checklist were collated using items from existing rating systems for quality of reporting (CONSORT, 2010) and methodological rigour (SIGN 50, 2011). Three

additional items (4, 6 and 16) were added by the author to reflect areas of importance to the studies included in the current review. By including only those items which relate to methodological quality (items 2, 5-8, 10, 12 and 13), the ratings of each of the papers included in the current review may more accurately reflect the ability of these to address the review question without the confound of reporting quality.

1.5.4 *Research Implications*

Overall, the findings suggest a consistent impairment in decision-making under ambiguity, using the IGT, in adults with alcohol-dependence. This was in keeping with findings from studies of other clinical populations who demonstrate similar real-life decision-making deficits; such as pathological gamblers, people with OCD, schizophrenia, ADHD, psychopathy, HIV, Huntington's Disease, Parkinson's Disease and eating disorders (Buelow and Suhr, 2009). This would suggest that the IGT is effective at detecting such impairments in an alcohol dependent population. However, the findings in relation to AD subgroups were less consistent. Therefore, it is recommended that further research into subgroups of alcohol dependent individuals be carried out with sufficient sample size to detect what may be subtle differences in performance and perhaps begin to uncover particular risk-factors for increased decision-making deficit in this heterogeneous population.

As aforementioned, the construct of decision-making as measured by the IGT may be better assessed by considering the early versus late stages of the task. Brand et al. (2007) referred to selections in the early phase of the IGT as decisions under ambiguity and those in the late phase as decisions under risk. In the earlier blocks, participants are unaware of the contingencies attached to each deck but, as the task progresses, they begin to learn these

and therefore to make decisions with more explicit understanding of the potential for loss. These processes have come to be known as ‘hot’ decision-making (under ambiguity and consistent with the somatic marker hypothesis) and ‘cold’ decision-making (under risk). Therefore, decisions at different stages of the task may be considered to be using different processes of decision-making. The findings of the current review would seem to support this conceptual split of the phases of the task as, overall, the deficit observed between AD groups and controls became greater as the task progressed. Therefore, it is possible that risky decisions made by AD individuals in the latter phase of the task indicate a more rational, ‘cold’ decision-making deficit. Therefore, research into the conceptual differences of the phases of the IGT in AD may be helpful in isolating the particular deficits in this population and informing more sophisticated approaches to care and treatment.

1.5.5 *Clinical Practice Implications*

Decision-making deficits are considered one of the hallmarks of addiction. Understanding of the processes underpinning these is essential in helping to break the destructive cycle of relapse. The findings would suggest benefit from providing support to AD individuals during any formal decision-making process, such as decisions related to welfare and finances. Given the possibility that AD individuals are less able to make use of ‘gut instinct’ or somatic markers, any process that serves to elucidate the options – and associated benefits or drawbacks of each – to the individual, may be of some assistance. Consistent with this idea, a systematic review of neuropsychological rehabilitation in ARBD suggests potential benefit of rule provision strategies in helping to provide structure during problem-solving situations (Svanberg & Evans, 2013). However, as discussed, even with explicit knowledge of potential loss and gain associated with decision-making situations, people with AD may

still struggle to make the advantageous choice. With regards to clinical or therapeutic input, a number of interventions related to relapse prevention involve elements of decision-making (e.g. decisional balance in Motivational Interviewing techniques, Miller and Rose, 2013). Patients must also make day-to-day decisions in relation to lifestyle choices and independent living which inevitably involve aspects of reward and consequence. It seems likely from the current review that people with AD may benefit from additional support in these tasks and perhaps assistance with planning for the future in a bid to overcome the temptation to resort to prepotent responses.

Furthermore, it may be of value for individuals with AD to acknowledge what may be considered to be a biologically-driven explanation for some of the difficulties they experience. The 'disease model' of addiction, for example, suggests that by seeing addiction as an illness the individual may learn to use the help available to them and to live in spite of their difficulties rather than strive to be rid of them (Cook, 1988). The findings of this review would suggest that decision-making deficits may be long-standing in this population and it is possible that they even pre-date problematic alcohol use. Therefore, for some, being able to identify with this may not only normalise their experience but also facilitate them in seeking support to manage their addiction.

1.5.6 *Conclusions*

This systematic review of decision-making deficit, as measured by the IGT, in an alcohol dependent population demonstrates that within the current literature there is considerable support for decision-making deficits in AD. Support was also found for a reduced level of improvement across the task in AD, which may be interpreted as a shift towards risky

decision-making. Evidence for factors influencing decision-making ability in this group was wide-ranging and demonstrated mixed results. History of conduct disorder and presence of antisocial personality traits may increase decision-making deficits in AD individuals.

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CHAPTER 2 EMPIRICAL PAPER

The Predictive Capacity of a Cognitive Screen: Can the Addenbrooke's
Cognitive Examination - III Predict Early Relapse Following Inpatient
Detoxification in Severe Alcohol Dependence?

(6075 words, excluding abstract and references)

Written in accordance with the author guidelines for submission to the journal *Drug and Alcohol Dependence*

(Author's Guidelines – see Appendix 1)

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2.1 ABSTRACT

Background: Much research has evidenced the negative impact of cognitive impairment on outcomes following treatment for addictions. Research specifically into alcohol-misusing populations is less consistent. The aims of the current study are to compile a normative dataset for a clinical sample of severely alcohol dependent adults in the early stages of abstinence, using the ACE-III cognitive screen, and to investigate the ability of the ACE-III to predict risk of relapse following treatment for alcohol dependence.

Methods: The current clinical sample was compared to existing normative data for the ACE-III. Predictive models were developed using relevant covariates to investigate the contribution of cognitive status to relapse at one-month.

Results: The study identified substantial cognitive impairment in a severely alcohol dependent population in the early stages following inpatient detoxification. No association was found between gender and ACE-III performance. Negative correlations were found between age and total ACE-III, memory, verbal fluency and visuospatial domains. Performance on the ACE-III was not predictive of relapse at one-month post-discharge. Associations were found between age and ACE-III score and between age and relapse. Age did not predict relapse.

Conclusions: These findings suggest that, following one week of abstinence, alcohol dependent individuals may exhibit a substantial degree of global cognitive impairment. Impairment did not however predict relapse in the current sample at this time. It is suggested that the ACE-III may not be sensitive to the full profile of cognitive impairment often seen in alcohol dependence. Limitations of the current study, implications for research and clinical practice are discussed.

Keywords: alcohol dependence, cognitive impairment, outcomes, relapse

2.2 INTRODUCTION

Alcohol dependence has been described as a chronic and relapsing condition (e.g. Stockwell, 1999). Many patients with alcohol dependence will relapse within one year of treatment (65-70%), with most relapsing within three months (e.g. Miller & Hester, 1986; Miller, Walters & Bennett, 2001). Various factors affecting relapse have been identified including depressive symptoms (Suter et al., 2011); anxiety (Willinger et al., 2002); self-efficacy (Blomqvist et al., 2003); gender (Zwyiak et al., 2006) and cognitive functioning (Morrison, 2011). Conversely, engagement with addictions treatment has been consistently associated with a favourable treatment outcome in substance use disorders (SUDs) (Brorson et al., 2013). In their systematic review of studies looking at risk factors for drop-out from addictions treatment, Brorson and colleagues identified the most consistent risk factors as cognitive deficits, low treatment alliance, personality disorder and younger age.

With such a range of variables impacting on the outcome of treatment for alcohol dependency, it is of great importance for specialist services to consider their approach to assessing and treating this problem. National government guidelines for the treatment of alcohol dependency highlight the importance of a comprehensive assessment which includes – amongst other things – assessment of readiness and belief in the ability to change; cognitive functioning; degree of dependence and psychological problems (NICE, 2011). Many treatments for alcohol dependence endorse a focus on relapse prevention and this is reflected in the Scottish Intercollegiate Network Guidelines (p 16; SIGN 74, 2003), which state that access to established relapse prevention treatment should be facilitated for all patients dependent on alcohol. With drop-out from treatment having clear ramifications for alcohol dependent individuals (and their wider networks), including

contributing to relapse, consideration of factors which may contribute to continued engagement with treatment services must also play a part in any process of assessment and treatment.

Given the vast scope of potential contributors to outcome in this population, it is unsurprising that a great deal of research has gone into identifying which of these factors is *most* predictive of relapse and/or drop-out from treatment. With regards to drop-out in particular, the recent review by Brorson et al. (2013) demonstrated that cognitive impairment would appear to be the most consistently associated with poor outcome in the field of substance misuse. A significant amount of research shows that harmful alcohol use can lead to impairments in cognitive function (e.g. Tapert et al., 2001). Such impairment can arise as a result of various factors, such as the direct result of the toxic effect of alcohol on the brain's neurophysiology (Oscar-Berman et al., 1997), injuries acquired as a result of intoxication (e.g. head injury; Galbraith et al., 1976), and even from the toxic effects of alcohol withdrawal (e.g. 'excitotoxicity', De Witte et al., 2003) and associated complications, such as withdrawal seizures (Loeber et al., 2010). Morrison (2011) found that specific cognitive impairments may also be seen as predictors of relapse, in particular, executive functioning. This has clear implications for the process of recovery from alcohol dependence and is further complicated by the fact that many of the interventions that are suggested for the management of harmful alcohol dependence – such as psycho-education and cognitive behavioural therapy (NICE, 2011) – require the development of skills which rely heavily on cognitive processes (e.g. Weinstein & Shaffer, 1993).

As a result of the high prevalence of cognitive impairment in the alcohol-misusing population, the National Institute for Health and Clinical Excellence (2011) recommends that cognitive functioning be assessed as part of a comprehensive assessment when adults are referred to specialist alcohol services. This, however, presents a number of challenges to the care provider. Firstly, it is well established that cognitive functioning is often impaired on commencing detoxification due to the aforementioned toxic effects of alcohol and withdrawal on the neurophysiology of the brain. Therefore assessing someone in the early stages of detoxification is likely to give a misrepresentation of their baseline abilities. Cognitive functioning has been found to improve following a few weeks of abstinence (Bates et al., 2002), with the greatest return of functioning happening within the first week (Ryan & Butters, 1986 cited in Lezak, 2004). It is generally recommended that cognitive assessment take place after 3-6 weeks of abstinence (Lezak, 2004). From a practical perspective however, there are difficulties in achieving this degree of abstinence in many patients with alcohol dependence. Whilst cognitive assessment carried out in the initial stages of detoxification may not provide an accurate longer-term estimate of functioning, it may provide valuable information about the patient's current level of functioning and subsequent ability to participate and engage in treatment. This may be one of the few opportunities available during which treatment may be offered. Furthermore, given time pressures on clinical staff, it is of relevance that any screening tool be time-efficient and suitable for use by a wide range of clinicians. There is evidence to suggest that cognitive impairment can affect both treatment outcomes (e.g. Fals-Stewart, 1993) and the ability to adhere to treatment programmes (Bates et al., 2006). Therefore, the impact of cognitive impairment, frequency with which it is observed in the alcohol dependent population and its potential role in contributing to poorer outcomes supports the consideration and assessment of cognitive functioning for patients entering treatment for their addiction.

Scottish Intercollegiate Guidelines Network (SIGN; 2003) guidelines highlight the need for simplified screening tools that help identify the issues that affect patients with alcohol dependence; however, there are very few brief, cognitive screening tools that have been validated for use with an alcohol dependent population. NICE (2011) suggest that the ACE-R (Addenbrooke's Cognitive Examination – Revised; Mioshi et al., 2006) may be sensitive enough to identify mild cognitive impairments in people who misuse alcohol. The ACE-R has been validated in a wide variety of populations including individuals with brain injury (Gaber, 2008); fronto-temporal dementia, Alzheimer's disease, mild cognitive impairment (Bak & Mioshi, 2007) and Parkinson's disease (Reyes et al., 2009). Developed as an 'extended MMSE' (Mini Mental State Examination; Folstein et al., 1975 – also suggested by NICE for use in screening for cognitive impairment in alcohol misuse), the original ACE was developed to cover a wide spectrum of cognitive functioning: attention and orientation, memory, fluency, language, and visuospatial abilities (Mioshi et al., 2006). Despite the tool's apparent sensitivity in detecting impairment in the above populations, there does not appear to have been any research carried out looking at the use of the ACE-R with an alcohol dependent population. The ACE-R has recently been updated to the ACE-III due to copyright issues related to the MMSE, which formed part of the ACE-R screening tool (Hsieh et al., 2013). The opportunity was also taken to modify some of the items which had presented relative weaknesses in the measure with a view to strengthening the tool's sensitivity and validity. Similar to its predecessor, there does not appear to have been any research carried out looking at the use of the ACE-III with an alcohol dependent population.

2.2.1 *Aims of the Study*

There is clearly a role for the effective identification of cognitive impairment in patients entering treatment for alcohol dependence. There is also sufficient justification for investigating brief, cognitive screening tools to identify such impairment of functioning. In 2007, The Scottish Government published a strategy document for the provision of care and support for people with co-occurring substance misuse and mental health problems ('Commitment 13', The Scottish Government, 2007). This document highlights the potential value of cognitive screens in forming part of a comprehensive assessment of alcohol-related brain damage (ARBD). The ACE-R had no normative data for the substance-misusing population; this is currently also the case for the ACE-III. Given the use of the tool in this population and its endorsement in national guidelines, it seems pertinent to be able to compare an individual's score to a more clinically-relevant data-set, allowing for potentially more meaningful comparisons to be made and to inform care planning. The aims of this study therefore are to present a normative dataset for the ACE-III in an alcohol dependent population (Part I) and to establish whether the ACE-III can identify those patients who are at most risk of drop-out from treatment and/or relapse (Part II). As a result of variations in data availability for each participant, Parts I and II of the current study involve different subsets of the overall sample (see section 2.3.1 for details of each).

2.3 **METHOD**

2.3.1 *Participants*

The present study was part of a larger service evaluation within the host site looking at the range of presentations and outcomes for those attending for inpatient detoxification from substance dependency. In the current study, only data from alcohol dependent (AD)

patients were used. Data were collected from November 2013 to August 2014. A total of 186 viable datasets were collected over this time period for people entering the clinic for alcohol detoxification. Of this number, 136 participants met inclusion criteria for the current study (see Table 1): 97 males (71.3%) and 39 females (28.7%). The average age was 47(±9.1) years for this particular cohort and average length of admission was 11.4 days (max. 30 days; 85% staying between 7 and 14 days). Participants who reported concurrent substance use in addition to alcohol were included in the analysis owing to the high degree of such substance use patterns in AD individuals (Staines *et al.*, 2001). The inclusion criteria were designed to be as broad as possible to maximise the ecological validity of any findings.

Table 1 – Reasons for Exclusion

Reason for Exclusion	Number of Participants
<i>Patient admitted for any reason other than, or in addition to alcohol detoxification (e.g. opiate conversion/reduction or respite)</i>	10
<i>History of traumatic brain injury</i>	2
<i>Known or queried intellectual disability</i>	1
<i>Formal diagnosis of alcohol-related brain damage</i>	2
<i>Unstable opioid use</i>	8
<i>Inpatient stay of less than 7 days</i>	21
<i>Formal diagnosis of polysubstance abuse</i>	3
<i>Invalid datasets (issues relating to comprehension of items on measures)</i>	3
<i>Total</i>	50

All participants met ICD-10 (World Health Organisation, 1992) classification for alcohol dependence and were deemed ‘severely’ dependent (as outlined in SIGN 74 guidelines,

SIGN, 2003) by virtue of their requirement for an inpatient detoxification, as opposed to community-based alternatives.

Two sub-samples were used for the separate parts of this study; N=73 for Part I and N=20 for Part II (see Table 2). All patients received treatment as usual: a reducing regime of benzodiazepine therapy to manage their withdrawal symptoms in combination with vitamin B therapy and a menu of psychosocial interventions including an inpatient group programme and access to a multi-disciplinary team. Dosage and duration of medications was varied depending on individual needs. Patients typically stay between seven and ten days for an alcohol detoxification.

Table 2 – Demographic and Patient Characteristics

Characteristic	Sample for Part I (N=73) ^a	Sample for Part II (N=20) ^b
Age – mean(SD)	46.83(9.25)	44.15(7.78)
Gender - % Female	34.2%	40%
Length of Admission		
- Range(days)	7-27	9-24
- Mean(SD)	11.96(3.85)	12.45(3.47)
Opioid Dependence	4.1%	5%
Benzodiazepine Dependence	9.6%	15%
Mood Problems	56.2%	65%
Anxiety Problems	21.9%	15%
Day ACE-III Administered (time from admission)	7-13	8-10
- Range(days)	8.52(1.03)	8.60(0.82)
- Mean(SD)		
Concurrent Illicit Drug Use	23.3%	20%

^a Sample comprised those datasets which included complete ACE-III data.

^b Sample comprised those datasets which included data for all predictor and outcome variables.

Explicit consent was not sought from participants in relation to the current study since patients consent to the use of their clinical data in relation to audit and service evaluation

at the point of admission. This was carried out in line with local policy and procedure and approval was granted for such use of data by the local Caldicott Guardian (see Appendix 6). Ethical approval was granted by the Ethics Committee at the School of Health in Social Science, University of Edinburgh (see Appendix 7). Informal advice was sought from a representative of the South East Scotland Research Ethics Service, who confirmed that the project constituted a service evaluation and therefore did not require NHS ethical review.

2.3.2 Procedure

As part of routine clinical practice, all patients were assessed by ward staff on admission to the clinic. Because previous research has identified a relationship between age, mood and anxiety with treatment outcomes, these formed the predictor variables in the current study. Alongside these variables, the importance of assessing readiness to change has been highlighted and was therefore included in the analysis. It is acknowledged that other variables have the potential to influence outcomes following treatment for alcohol-dependence (see Adamson et al., 2009 and Brorson et al., 2013 for systematic reviews). Owing to practical constraints on the current project – specifically, that data were collected in line with routine clinical practice – it was not feasible to include other potential confounders. Given the exploratory nature of the study however, this was deemed satisfactory.

Information regarding patient age, mood, anxiety and motivation was routinely collected as part of a clinical interview at the time of admission. At a minimum of seven days following admission, and therefore seven days of abstinence, all patients attending for alcohol detoxification were invited to take part in an ACE-III assessment by a member of the ward

staff. It was not possible or clinically appropriate to assess all patients at precisely seven days following admission owing to variations in individual needs and clinical practicality. It was decided, in keeping with recommendations from clinical neuropsychological literature, that data would be viable for the current project so long as the ACE-III took place at a *minimum* of seven days abstinence from alcohol (that is, seven days from the point of admission).

All routinely collected data were entered into an excel database. Only the information relevant to the current study was extracted to conduct relevant analyses. Follow-up data were obtained via email to patient keyworkers sent by the lead clinician for the clinic.

2.3.3 *Measures*

2.3.3.1 *Mood and Anxiety*

The presence of a comorbid mood or anxiety disorder was assessed via three sources: clinical interview on admission (nursing and medical review), clinical assessment during inpatient stay, and whether or not the patient was using anti-depressant medication at the time of admission. It is widely acknowledged that alcohol misuse has a depressant effect and therefore it is impossible at this early stage of treatment to know whether mood disorder – separate to that caused by alcohol use – is, in fact, present (Davidson, 1995). Furthermore, research would suggest that most anxiety and depression resolves with standard treatment for alcohol problems (see SIGN 74, 2003). In light of this, it was not deemed viable to introduce formal mood or anxiety measures into routine practice. Therefore, the proxy measures noted above were adopted for the current study. If an

individual met any one of the three above-noted criteria, mood or anxiety disorder was coded as present.

2.3.3.2 *Motivation*

The Revised Readiness to Change [Treatment Version] Questionnaire (RCQ[TV]) is a twelve-item, self-report measure of motivation to change drinking behaviour (Heather & Hönekopp, 2008). Based on the transtheoretical model of health behaviour change (Prochaska *et al.*, 1992), the items in the questionnaire are designed to assess which stage of change the client is at, at the point of administration: pre-contemplation, contemplation or action. Each item features a statement related to the client's beliefs about their drinking behaviour. They respond using a five-point Likert scale, ranging from 'strongly disagree' to 'strongly agree', with scores for each item ranging from -2 to +2. Four items relate to each of the stages of change and therefore a total score for each stage may be calculated; with the highest score denoting the stage of change the client is thought to be at (quick scoring method; Heather *et al.*, 1999). Although this measure is self-report, assessing clinicians assisted clients in its administration to ensure completeness and help reduce issues related to literacy and comprehension.

The RCQ[TV] has demonstrated good internal consistency across the three subscales and good construct validity, as established by strong correlations with measures of alcohol use and alcohol-related problems (Heather & Hönekopp 2008) and between RCQ[TV] subscales and a measure of negative outcome expectancies for alcohol treatment. The authors also reported significant relationships between stage of change as measured by the RCQ[TV] and treatment outcome at three and 12 months, suggesting the predictive validity of the

tool. The internal consistency of the subscales in the current study were assessed for the sample used in Part II, demonstrating reasonable reliability (pre-contemplation: N=4, $\alpha=.794$; contemplation: N=4, $\alpha=.714$; action: N=4, $\alpha=.723$).

2.3.3.3 *Cognitive Functioning*

The Addenbrooke's Cognitive Examination III (ACE-III; Hsieh *et al.*, 2013) is a revised and updated version of the widely-utilised Addenbrooke's Cognitive Examination Revised (ACE-R) (Mioshi *et al.*, 2006). The tool assesses five cognitive domains: attention, memory, language, fluency and visuospatial abilities. The tool is scored out of 100, with higher scores denoting better cognitive functioning. Domain-specific scores may also be calculated and compared with published norms for a healthy older adult population ($n=25$; Hsieh *et al.*, 2013). Hsieh and colleagues demonstrated a strong correlation ($r=0.99$) between the ACE-III and its predecessor. They also reported that the domain scores achieved medium to high correlations with neuropsychological tools commonly used in the assessment of dementia, suggesting good construct validity. The sensitivity and specificity of the tool in relation to dementia remain high relative to the cut-off scores suggested by the original authors (88/100 and 82/100, respectively), with its internal reliability proving robust (Cronbach's alpha coefficient = 0.88).

2.3.3.4 *Relapse*

In line with other research looking at outcomes following treatment for substance misuse, it was originally planned that drinking outcomes would be measured in three ways: cumulative days of abstinence, time to first drink and number of days drinking. However, it was not possible to obtain this information at four-week follow-up and therefore the

dichotomous variable of 'relapsed' versus 'abstinent' was utilised instead. The operational definition of relapse in this instance would include any return to alcohol, as reported by the participant's keyworker. Where participants failed to engage with treatment – and also in line with other research (e.g. Schneekloth, 2012) – they were presumed relapsed.

2.3.3.5 Engagement

Following discharge from the clinic, patients are allocated a keyworker. The outcome measure for engagement was originally planned to be a proportion of appointments attended compared to those offered, calculated as a percentage. However, due to limited information and variability in follow-up data returned, it was decided that a dichotomous variable of less than 50% versus 50% or more would be adopted. Following an investigation of the descriptive characteristics of this sample, it was identified that this variable had no variability, with all 20 participants attending 50% or more appointments offered. It was therefore removed from further analysis.

2.3.4 Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS), Version 22 (IBM SPSS, 2013). For Part I of this study, mean scores and standard deviations were calculated for the total ACE-III score and its subdomains. Shapiro-Wilk test of normality indicated non-normal distributions, therefore Mann Whitney U tests were used to compare ACE-III scores between males and females and Spearman's Rho correlations were used to examine associations between age and ACE-III. For Part II, descriptive statistics (means, standard deviations and frequencies) were used to describe the characteristics of the smaller sample. Tests of normality indicated that age and ACE-III

total score distributions did not deviate significantly from a normal distribution so independent samples t tests were used to examine differences in age and ACE-III score between those who relapsed at four weeks post-discharge and those who had not. Chi square analysis was used to investigate differences between the categorical predictor variables (mood, anxiety, motivation) in relation to relapse status. Logistic regression was used to examine the relative contribution of the predictor variables to relapse status. Using the conventional method for sample-size calculation in regression analysis (reported in Green, 1991): $N \geq 50 + 8 m$; it is estimated that a sample size of greater than 90 participants would be required to meet statistical power in the current analysis.

2.4 RESULTS

2.4.1 *Part I: Clinical Normative Data*

The cohort used to compile the normative dataset consisted of 73 alcohol dependent individuals aged between 23 and 72 years. Of these participants, 48 were male. With regards to other substance use, 3 individuals were known to be opioid dependent but stable in their opioid use and 7 were benzodiazepine dependent. Fifty-two reported no concurrent use of other substances at the time of their assessment. The remainder reported varying types and degrees of substance use.

The alpha coefficient of the ACE-III in this study was 0.82, which is comparable to the values found for the original ACE-R (0.80; Mioshi et al., 2006) and the ACE-III (0.88; Hsieh et al., 2013) and considered acceptable (Field, 2005). Table 3 presents domain and total ACE-III scores for the current sample alongside the normative data published using a sample of 25 healthy older adults with an average age of 66.1 (SD=7.4; Hsieh et al., 2013). The table also

includes the 'lower limit of normal', calculated as described in the study of the earlier ACE-R (Mioshi *et al.*, 2006), which was taken to be the total score minus two standard deviations.

Table 3 – ACE-III Total and Domain Scores: Mean(SD)

Study	Attention/ Orientation	Memory	Verbal Fluency	Language	Visuo- spatial	ACE-III Total
<i>Hsieh et al. (2013)</i> <i>N=25</i>	17.4(1.2)	24.3(1.7)	12.5(1.4)	25.6(0.6)	15.6(0.6)	95.4(3.3)
<i>Lower limit of normal</i>	15	20.9	9.7	24.4	14.4	88.8
<i>Current study – Whole Sample (N=73)</i>	16.3(1.8)	20.0(4.4)	9.6(2.7)	23.5(2.3)	13.8(2.2)	83.2(10.1)
<i>Current study – Females (N=25)</i>	15.9(1.8)	20.3(4.8)	9.1(2.7)	23.1(2.3)	13.4(2.3)	81.8(11.1)
<i>Current study – Males (N=48)</i>	16.5(1.7)	19.9(4.2)	9.9(2.7)	23.7(2.3)	14.0(2.1)	83.8(9.6)

As can be seen, the AD sample in the current study scored more than two standard deviations below the healthy normal sample on all domains except attention/orientation (<1SD below normative mean). For the memory and fluency domains, the clinical sample fell less than three standard deviations below the healthy control mean. For the visuospatial domain, scores fell exactly three standard deviations below the control mean and, for language, greater than three standard deviations. The largest deficit was observed for the overall score, where the clinical sample score fell 3.7 standard deviations below the healthy control mean.

2.4.1.1 *Gender Differences on ACE-III Scores*

Mann Whitney U tests indicated no significant differences between males and females on ACE-III Total score ($U=541.00$, ns, $r=-.08$), Attention/Orientation ($U=482.00$, ns, $r=-.17$), Memory ($U=567.50$, ns, $r=-.04$), Verbal Fluency ($U=467.00$, ns, $r=-.18$), Language ($U=495.50$, ns, $r=-.14$) or Visuospatial domains ($U=510.50$, ns, $r=-.12$).

2.4.1.2 *Correlations between Age and ACE-III Scores*

There was a negative relationship between the age of participants and ACE-III Total score, $r_s=-.368$, $p=.001$. A negative relationship was also found between age and scores for Memory ($r_s=-.384$, $p=.001$), Verbal Fluency ($r_s=-.447$, $p<.001$) and Visuospatial domains ($r_s=-.268$, $p=.0023$). No relationship was identified between age and scores on Attention/Orientation or Language (both $p>.05$).

2.4.2 *Part II: Predictors of Outcome*

The sample used for Part II of this study comprised 20 alcohol dependent individuals aged between 23 and 56 years (average 44.2, $SD=7.8$). Twelve participants were male. One participant was opioid dependent and three were dependent on benzodiazepines. Four reported illicit drug use in addition to alcohol use.

2.4.2.1 *Associations between Predictor Variables and Relapse*

The difference between continuous predictor variables in relation to relapse status (relapse having two levels: 0=relapsed, $N=7$; 1=abstinent, $N=13$) was assessed using independent

samples t-tests. Relapsed individuals were significantly older (49.14 ± 4.71 years) than those who remained abstinent at four weeks post-discharge (41.46 ± 7.90 years), $t(18) = 2.341$, $p = .031$. There was no significant difference in ACE-III score between those who relapsed (85.29 ± 8.64) and those who remained abstinent (88.46 ± 9.09), $t(18) = -.758$, $p = .458$. Differences in domain scores between those who relapsed and those who remained abstinent were also non-significant (attention: $U = 49.00$, ns, $r = -.06$, memory: $U = 62.00$, ns, $r = -.30$, fluency: $t(18) = -0.223$, $p = .826$, language: $U = 61.50$, ns, $r = -.29$, visuospatial: $U = 42.00$, ns, $r = -.06$).

The difference between categorical predictor variables in relation to relapse status was assessed using Pearson's chi-square test. No group differences were identified between mood and relapse, $\chi^2 = 2.32$, $p = .128$; anxiety and relapse, $\chi^2 = .00$, $p = .948$; or motivation and relapse, $\chi^2 = .85$, $p = .357$.

2.4.2.2 *Predictors of Relapse*

For exploratory purposes, despite low sample size, a logistic regression analysis was undertaken to predict relapse in this sample using age, mood, anxiety, motivation and ACE-III score as predictors. A test of the full model against a constant-only model demonstrated statistical significance, indicating that the predictors – as a set – reliably distinguished between those who relapsed and those who remained abstinent (chi square = 17.963, $p < .01$, $df = 5$). The model explained 81.6% (Nagelkerke's R square) of variance in relapse and correctly classified 95% of cases. The Wald criterion demonstrated that no individual predictor variable contributed significantly to the model (all $p > .05$).

Because age was found to be associated with relapse, a separate logistic regression was undertaken to predict relapse using age as the only predictor variable. A test of the full model against a constant-only model demonstrated statistical significance of the model (chi square = 6.293, $p < .05$, $df=1$) which explained 37.2% (Nagelkerke's R square) of variance in relapse and correctly classified 70% of cases. The Wald criterion demonstrated that age did not contribute significantly to the model ($p > .05$).

2.5 DISCUSSION

2.5.1 *Summary of Findings*

The first aim of this study was to compile a normative dataset for an alcohol dependent population, using the ACE-III, following one week of abstinence. The clinical sample scored 3.7 standard deviations below published norms on the ACE-III overall. Sub-domain scores also indicated reduced functioning compared to norms for all domains except attention/orientation, where the score fell within the normal range. Negative correlations were found between age and scores on overall ACE-III, memory, verbal fluency and visuospatial domains.

The second aim of the study was to investigate the predictive capacity of the ACE-III in relation to engagement with treatment and relapse following inpatient detoxification. ACE-III scores were not significantly different in those who relapsed compared to those who did not. Those who relapsed were older than those who did not. No associations were found between mood, anxiety, motivation (RCQ[TV]) and relapse. Logistic regression revealed no relationships between any of the predictors and relapse.

2.5.2 *Interpretation of Findings – Normative Data*

The finding that the current clinical sample performed below a healthy control sample on the ACE-III cognitive screen is unsurprising. What makes this more striking is that the comparison group were, on average, twenty years older than the clinical sample presented here. A strong body of research would suggest that AD individuals consistently exhibit cognitive impairment compared to their peers on a wide variety of neuropsychological functions (Parsons, 1998). These deficits tend to be most apparent in the areas of memory and visuospatial functioning, which is consistent with the current findings. However, language abilities tend to be relatively well preserved in alcohol-dependence (Hartman, 1995; cited in Hazelton, 2003) and, in this sample, language performance fell significantly below what might be expected. Despite its ability to briefly measure a wide variety of domains of cognitive functioning, the ACE-III is heavily weighted towards tasks of language ability (Hsieh et al., 2013). Therefore, it is surprising that the current sample exhibited marked impairment in this area.

It is possible that the early stage of assessment in this study uncovered a profile of difficulties that are present in the earlier stages of abstinence and differ from that in longer-term abstinence. The ACE-III was administered between seven and eleven days in the current study, falling far short of the recommended three-week minimum. Therefore it is likely that the assessment picked up a degree of residual impairment owing to prior intoxication and the detoxification process itself. The reducing regime of benzodiazepine therapy during detoxification is adjusted according to the needs of the individual and therefore, at the time of the cognitive screen, it is possible that participants were at varying degrees of abstinence from prescribed medication. Benzodiazepines are known, in

particular, to reduce memory and learning ability (Stewart, 2005) alongside having the effect of sedation. It is possible that this and concurrent drug use in a proportion of the sample contributed to the profile of impairment observed.

Whilst no formal measure of dependence severity was used, it is likely that the majority of participants in this study would fall within the severe range. Furthermore, since no measure of premorbid functioning was used, it is possible that overall intellectual ability was lower in this sample. Illiteracy levels tend to be higher within substance-using populations than in the general population and this may go some way to explaining the reduced performance in tasks of language functioning. The purpose of presenting a normative dataset was to allow for clinical comparisons of ACE-III performance in a severely alcohol dependent population in the early stages following detoxification. Whilst limited in their generalisability beyond this population, it is hoped that the presented data allow for more meaningful comparisons in this particular client group.

2.5.3 *Interpretation of Findings – Predictors of Outcome*

The findings from the current study do not support the idea that ACE-III scores predict relapse. However, it is important to bear in mind the low sample size and consequent low power achieved in the statistical analyses involved in this part of the study (see section 2.5.4 below for discussion of implications). This is surprising in the context of a large body of research supporting a relationship between cognitive functioning and treatment outcomes in addictions. One possible reason for this discrepancy is the choice of measure of cognitive functioning. Whilst the ACE-III has been recommended for use in the alcohol dependent population, its suitability for assessing alcohol-related cognitive impairment has

not been investigated. Alcohol dependent populations tend to show marked impairment on tests of executive functioning, even in the absence of other neuropsychological and functional impairment (Moselhy et al., 2001). This was reflected in the current sample by scores averaging more than two standard deviations below the normative mean for the verbal fluency domain. This domain however, is the only one in the ACE-III thought to rely substantially on executive functioning and its relative contribution to the overall score is small (14 of 100 possible points). Given the prevalence of executive dysfunction in this population and the likely impact of this on ability to engage in psychosocial interventions, it would be of relevance to consider cognitive screening tools which place more emphasis on this particular area of functioning. Furthermore, executive functions are believed to serve the role of overseeing and controlling the primary cognitive functions (Stuss, 2011). From this perspective, it is possible that some degree of impairment across tasks of other domains of functioning may result from executive functioning deficits rather than domain-specific deficits. A study of neuropsychological functioning and relapse in a similar population to the current study identified that executive dysfunction during detoxification successfully predicted number of days drinking at three months post-discharge (Morrison, 2011). A systematic review of risk factors for drop-out from treatment in addictions also highlighted that executive functioning deficits were often what distinguished those who engaged with treatment from those who did not (Brorson et al., 2013). These findings highlight the need to include a measure sensitive to such functioning in any assessment of alcohol-related cognitive impairment.

Another aspect of the current study which may have resulted in finding no relationship between ACE-III score and outcome was the method of recording follow up. Owing to

limited information available, the outcome variable of relapse was dichotomised to allow for retention of data. The normative data presented for this clinical sample demonstrated a greater degree of variance in ACE-III scores compared to the healthy comparison group, highlighting heterogeneity amongst substance-misusing populations. Miller et al. (2001) caution against dichotomising relapse data, as it does not take into account the degree of improvement often seen in a proportion of people who do not maintain abstinence but also do not return to drinking at their previous level. By reducing the outcome measure in this way, any relationship between cognitive functioning and outcome may have been obscured.

Finally, the current study examined the relationship between cognitive functioning and outcome in only severely alcohol dependent individuals. Whilst helping to create a 'purer' sample which, it was hoped, could be more comparable to similar clinical populations, it is acknowledged that such sampling may have limited the applicability of the research into outcomes which informed the current study. Of the 11 studies reviewed in relation to cognitive functioning and drop-out, Brorson et al. (2013) reported significant relationships in all of them. However, none of these reported on an alcohol dependent sample – five reported on mixed substance-use disorders, one on marijuana, four on cocaine and one on heroin and crack cocaine. Adamson et al. (2009) systematically reviewed the literature for predictors of alcohol treatment outcome and found neuropsychological functioning to be a moderate predictor, however they stated that the neuropsychological variables varied too much to draw any meaningful summary. These findings would suggest that the predictive capacity of cognitive functioning in 'pure' alcohol-dependence is not as clearly defined as in

wider substance-using populations. Furthermore, means of successfully capturing this impairment have not been clearly defined.

2.5.4 *Limitations*

One of the key limitations was sample size, particularly in relation to part II. Although it is tempting to suggest that a larger sample size may unearth a significant finding, none of the predictor variables in the analyses were even approaching significance. However, it is possible that reduced statistical power has prevented observation of trends toward significance which might otherwise have been apparent with a larger dataset. At the very least, with increased power it would have been possible to have greater confidence in the accuracy of the outcomes obtained in the current study. In addition, methods for collecting some of the information have added a considerable degree of confound to the data; for example, broad inclusion criteria and relying on key worker feedback to assess for relapse. Nonetheless, the large proportion of missing data in the current service evaluation serves to highlight the need for good quality recording of clinical information.

Whilst keyworkers supplied a reasonable degree of information, a high volume of missing data resulted in the loss of datasets and the eventual digression towards a dichotomous variable. This was particularly evident in relation to information on engagement with treatment. It may be that by including more assertive follow-up techniques, such as those suggested by the developers of the Addiction Severity Index ('Addiction Severity Index Manual and Question by Question Guide', The University of Pennsylvania, n.d.), and acknowledging the follow-up input of a wider range of supports and services, more sophisticated and reliable outcome data could be achieved.

2.5.5 *Implications for Research*

With the advent of the notion of ‘recovery capital’ – the sum of internal and external resources that can be drawn on by the individual to initiate and sustain recovery – , the potential value of social and mutual aid supports has become apparent in the field of addictions research (Best & Laudet, n.d.). Future research may benefit from including such variables and considering wider factors in addition to patient-specific variables, as suggested by Brorson et al. (2013). The current study included five predictor variables; however it is important to note that other variables have been demonstrated to contribute to treatment outcomes. These include – but are not restricted to – dependence severity, psychopathology, alcohol-related self-efficacy and treatment goal (Adamson et al., 2009); treatment alliance and personality (Brorson et al., 2013). It seems relevant to suggest that efforts go into separating those factors which are specific to alcohol dependent populations and working towards conceptual clarity and consistency of measurement and reporting of variables. In a population such as alcohol-dependency, which is so heterogeneous in nature, such methodological aspects become ever-more important to allow for meaningful interpretation of findings.

2.5.6 *Implications for Clinical Practice*

The findings highlight the need for a comprehensive assessment of cognitive functioning to inform treatment planning, with adequate emphasis placed on assessment of executive functions. It is clear from the normative data that in the early stages following detoxification, severely alcohol dependent individuals are likely to exhibit a substantial degree of cognitive impairment. The implications in terms of engaging with psychosocial

interventions are clear and it is important that treatment providers consider this in the planning and delivery of services for this population.

A recent systematic review by Svanberg and Evans (2013) outlined the evidence-base for the rehabilitation of alcohol-related brain damage, including executive dysfunction. If alcohol dependent individuals are to engage with and benefit from evidence-based psycho-social interventions, it is suggested that treatment programmes for such populations incorporate strategies for cognitive rehabilitation. This should also take into account adequate modification of patient environments to account for some of the difficulties this population face, such as clear signage to assist with orientating to a new environment. It is also suggested that if clinical populations such as the one accessed for the current study are to benefit from treatment, perhaps longer periods in contact with services with more intensive support will be required. Alcohol-related brain damage is sometimes referred to as 'alcoholic dementia' (see Moriyama et al., 2006). Older adult services in the UK often adopt a tiered service model, including day services for people with dementia. Perhaps then, given the degree of overlap in presentations between older adult dementia populations and alcohol dependent individuals, such models could afford a degree of insight into ways of working to enhance adherence to and efficacy of treatment for alcohol-dependence.

2.5.7 *Conclusions*

The current study identified a substantial degree of global cognitive impairment in a severely alcohol dependent population in the early stages following inpatient detoxification though this impairment was not found to be predictive of relapse at one-month following

discharge. Methods for recording outcome variables may have reduced the quality of this study. It is also noted that the ACE-III may not be sensitive to profile of impairment in this population. It is suggested that future research focus on identifying the factors specific to alcohol dependent individuals in relation to relapse, taking into account factors in addition to patient-related variables. Furthermore treatment providers should consider routinely assessing cognitive impairment in this population and tailor their input accordingly, both at a service and individual level.

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APPENDIX 1. AUTHOR GUIDELINES

DRUG AND ALCOHOL DEPENDENCE

An International Journal on Biomedical and Psychosocial Approaches

AUTHOR INFORMATION PACK

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DESCRIPTION

Drug and Alcohol Dependence is an international journal devoted to publishing original research, scholarly reviews, commentaries, and policy analyses in the area of **drug, alcohol and tobacco use and dependence**. Articles range from studies of the chemistry of **substances of abuse**, their actions at molecular and cellular sites, *in vitro* and *in vivo* investigations of their biochemical, pharmacological and behavioural actions, laboratory-based and clinical research in humans, substance abuse **treatment and prevention** research, and studies employing methods from epidemiology, sociology, and economics.

The rationale for this extensive coverage is the conviction that drug, alcohol and tobacco use/dependence cannot be understood in their entirety from a single perspective and that without an understanding of other areas of research, studies by individual investigators may be limited. The goal of the journal is to provide researchers, clinicians, and policy makers access to material from all perspectives in a single journal in a format that is understandable and which has received rigorous editorial review. The hope of its editors is to promote mutual understanding of the many facets of drug abuse to the benefit of all investigators involved in drug and alcohol research, and to facilitate the transfer of scientific findings to successful treatment and prevention practices.

The accepted abbreviation for *Drug and Alcohol Dependence* for bibliographic citation is *Drug Alcohol Depend.*

Drug and Alcohol Dependence is currently being distributed to all the members of the College on Problems of Drug Dependence (CPDD), the oldest scientific organization in the United States concerned with research on problems of drug dependence. Members of the CPDD are provided with both the print version as well as access to the full text of the

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INTRODUCTION

Drug and Alcohol Dependence is an international journal devoted to publishing original research, scholarly reviews, commentaries, and policy analyses in the area of drug, alcohol and tobacco use and dependence. It is sponsored by the College on Problems of Drug Dependence (CPDD), the oldest scientific organization in the United States concerned with research on addiction. The goal of its editors is to promote mutual understanding of the many facets of drug abuse to the benefit of all investigators involved in drug and alcohol research, and to facilitate the transfer of scientific findings to successful treatment and prevention practices. *Drug and Alcohol Dependence* is currently being distributed to all the members of CPDD.

Types of paper

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APPENDIX 2. MEASURING OUTCOMES IN THE IOWA GAMBLING TASK (IGT)

The Iowa Gambling task offers the researcher or clinician a variety of options for measuring outcome. Perhaps the most commonly cited in the research literature is net outcome for the total task (either monetary amount at end of task, number of cards picked from advantageous decks, or number of cards picked from advantageous decks minus those from disadvantageous ones). This measure allows for an overall estimation of the participant's decision-making ability taking the task as a whole (e.g. across the full 100 card selections). The benefits of this approach include that it allows for a simple judgement of an individual's ability and easy comparison of outcomes between groups of participants (see reviewed articles for examples). One clear disadvantage of this outcome measure however, is the lack of detail regarding choice behaviour over time.

Another common outcome measure derived from the IGT is to consider participants' performance at different temporal stages of the task (e.g. across each of the five blocks of 20 card selections or comparing early versus late stages). Similar to the net outcome approach, this can take the form of number of choices from advantageous minus disadvantageous decks within any given block. This particular method has been adopted widely in the literature examining IGT performance and yields some clear benefits over the total net score alone. Firstly, it allows the examiner to observe any patterns in performance across the task. Bechara, Tranel and Damasio (2000)¹ describe the implicit learning evident in healthy 'normal' individuals as demonstrated by an eventual shift towards so-called advantageous decks. By examining different stages of the task, the researcher may begin to see patterns of responding that give clues to the decision-making behaviour of the participant over time. Subsequently, this allows for consideration of the constituent processes at play throughout the different stages of the task. Given the known impact of alcohol-dependence on memory and aspects of learning, this would be of particular relevance to studies of any such populations and therefore has been included in the current review where this information was available.

In addition to the above outcome measures, many investigators have attempted to assess implicit 'learning' in the IGT. Dunn et al. (2006)² provide a critical evaluation of so-called 'somatic markers' where performance on the IGT is linked to autonomic physiological responses (skin conductance), which are thought to indicate the anticipation of failure or punishment on the task and tend to be absent in people with damage to the ventromedial prefrontal cortex. It is commonly accepted that, as the IGT progresses, participants gain more explicit or conceptual knowledge of the reward schedules of each deck (see Brand et al., 2007)³. Continuing to make disadvantageous decisions in the latter stages of the IGT is

¹ Bechara, A., Tranel, D. & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*, 123, 2189-2202.

² Dunn, B. D., Dalgleish, D. & Lawrence, A. D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Behavioral Reviews*, 30, 239-271.

³ Brand, M., Recknor, E. C., Grabenhorst, F., Bechara, A., 2007. Decisions under ambiguity and decisions under risk: Correlations with executive functions and comparisons of two different gambling tasks with implicit and explicit rules. *Journal of Clinical and Experimental Neuropsychology*. 29(1), 86-9

often considered 'risky' decision-making, owing to the assumed knowledge of the risks related to such choice behaviour. However, much debate exists in the research literature regarding the underlying processes of such behaviour owing to the low specificity of the IGT in this regard (Brand et al., 2007). Aspects of implicit learning were not directly related to the objectives of the current review and therefore have not been discussed.

APPENDIX 3. TABLE OF EXCLUDED PAPERS

Study	Reason(s) for exclusion
Alfonso <i>et al.</i> (2011)	Mixed substance-use disorder (SUD) group (alcohol, cocaine, cannabis)
Andrade & Petry (2012)	Mixed SUD group and <100% of those using alcohol met criteria for alcohol-dependence (AD)
Ashenhurst, Jentsch & Ray (2011)	Alcohol Use Disorder (AUD) group mixed AD (72.3%) and 'problematic drinkers'
Barry & Petry (2008)	Mixed SUD group
Bechara <i>et al.</i> (2001)	Mixed SUD group
Bishara <i>et al.</i> (2009)	No alcohol group
Bjork <i>et al.</i> (2008)	Alcohol patients co-dependent on/using 1 or more other substances
Bjork, Smith & Hommer (2008)	Alcohol patients co-dependent on/using 1 or more other substances
Boettiger <i>et al.</i> (2007)	Explicit decision-making (DM) measure used
Brand <i>et al.</i> (2005)	Explicit DM measure used
Brand <i>et al.</i> (2009)	Explicit DM measure used
Campbell, Samartgis & Crowe (2013)	SUD status (other than alcohol) not reported/excluded
Cantrell <i>et al.</i> (2008)	History of substance-use other than alcohol in AD group
Chanraud <i>et al.</i> (2007)	No DM measure
Claus & Hutchison (2012)	Only 74% of AUD group met criteria for AD
Corbin & Counce (2007)	Alcohol sample not assessed to have AD Explicit DM measure used
Courtney <i>et al.</i> (2012)	Only 71.9% of AUD group met criteria for AD
Dao-Castellana <i>et al.</i> (1998)	No DM measure
Demir <i>et al.</i> (2002)	No DM measure
De Wilde <i>et al.</i> (2013a)	AUD group polysubstance-dependent on at least three other substances
De Wilde <i>et al.</i> (2013b)	AUD group polysubstance-dependent on at least three other substances
Dom <i>et al.</i> (2006a)	History of polysubstance use/dependence in AUD sample
Dom <i>et al.</i> (2006b)	History of polysubstance use/dependence in AUD sample
Dom <i>et al.</i> (2007)	History of polysubstance use/dependence in AUD sample
Durazzo <i>et al.</i> (2006)	No DM measure
Fein <i>et al.</i> (2006)	Duplicate IGT results – already reported in Fein, Klein & Finn (2004)
Fernandez-Serrano <i>et al.</i> (2010)	Mixed SUD group
Fishbein <i>et al.</i> (2007)	Explicit DM measure used
Flannery <i>et al.</i> (2007)	Explicit DM measure used
Fridberg, Gerst & Finn (2013)	Mixed SUD group
Fukunara <i>et al.</i> (2013)	Mixed SUD group
Gansler <i>et al.</i> (2000)	No DM measure
Georgemiller <i>et al.</i> (2013)	Proportion of AD subjects exhibited polysubstance dependence
Gonzalez, Bechara & Martin (2007)	History of polysubstance use/dependence in AUD sample
Gullo & Stieger (2011)	AUD group not dependent
Harvanko <i>et al.</i> (2012)	Alcohol abuse and AD combined into one category
Hildebrandt <i>et al.</i> (2006)	Substance-use status of AD group not explicitly addressed
Jokisch <i>et al.</i> (2014)	No explicit exclusion of polysubstance use/dependence
Jollant <i>et al.</i> (2007)	High psychiatric comorbidity in sample Mixed SUD
Kamarajan <i>et al.</i> (2012)	AD sample known to include participants with comorbid drug abuse
Lawrence <i>et al.</i> (2009)	Explicit DM measure used
Lee <i>et al.</i> (2013)	DM measured in terms of reaction time rather than risky performance
Luhar <i>et al.</i> (2013)	No DM measure
Mazas, Finn & Steinmetz (2000)	History of substance-use other than alcohol in AD group
Mitchell <i>et al.</i> (2005)	Explicit DM measure used
Mitchell <i>et al.</i> (2007)	Explicit DM measure used
Rustemeier <i>et al.</i> (2014)	Explicit DM measure used
Stojek <i>et al.</i> (2014)	Explicit DM measure used
Stout <i>et al.</i> (2005)	Mixed SUD group
Tanabe <i>et al.</i> (2013)	Mixed SUD group
Van der Plas <i>et al.</i> (2009)	Occasional other substance use in proportion of AD group
Vanes <i>et al.</i> (2014)	Explicit DM measure used
Yechiam <i>et al.</i> (2008)	No alcohol group

APPENDIX 4. QUALITY CRITERIA CHECKLIST

Methodology Checklist	
<i>Author(s):</i> <i>Date:</i> <i>Title:</i>	
Scoring criteria: Yes = 1 point, No/Unclear = 0	
Item	Score
1. The study context and rationale is clear	
2. The aims of the study are specific and appropriate	
Participants	
3. Recruitment strategy is clearly defined	
4. Ethical considerations are described (including informed consent)	
5. 'Caseness' of participants is clearly defined	
6. Control group included	
7. Exclusion criteria are clear and applied to both cases and controls, where applicable	
8. Cases and controls are selected from comparable populations, where applicable	
Assessment	
9. Methods clearly described to allow for replication	
10. Potential confounding factors are acknowledged and adequately controlled for in the design and analysis	
Analysis and Results	
11. Descriptive statistics are presented	
12. A priori sample size calculation described	
13. Analysis is appropriate to the research aims	
14. Effect sizes are reported for measures of decision-making	
15. Confidence intervals are stated for outcomes related to decision-making	
Conclusions	
16. Results are clearly summarised in relation to the original aims/hypotheses	
17. Any conclusions are consistent with the results of the study and substantiated with relevant evidence	
18. Issues of generalisability and implications of the research are discussed	
19. Limitations are acknowledged	
Quality index (total score)	

APPENDIX 5. QUALITY RATINGS TABLE

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total score
Ando et al. (2012)	+	?	?	+	+	-	+	+	?	?	?	-	+	-	-	+	+	+	+	10
Bowden-Jones et al. (2005)	+	+	?	+	+	+	?	?	?	-	+	-	+	-	-	+	+	+	-	10
Brevers et al. (2014)	+	+	?	+	+	+	?	?	+	+	+	-	+	+	-	+	+	?	-	12
Cordovil De Sousa Uva et al. (2010)	+	+	+	+	+	+	?	+	+	+	+	-	+	+	-	+	+	+	+	16
Fein, Klein Finn (2004)	+	+	+	+	+	+	+	+	+	+	+	-	+	-	-	+	-	+	+	15
Fein, McGillivray & Finn (2006)	+	+	+	+	+	+	+	+	?	+	+	-	+	-	-	+	+	+	+	15
Goudriaan et al. (2005)	+	+	-	+	+	+	?	?	+	+	?	-	+	+	-	+	+	+	+	13
Kim, Lee & Kim (2006)	+	+	?	+	+	+	+	?	?	-	+	-	?	-	-	+	?	-	+	9
Kim, Sohn & Jeong (2011)	+	+	?	+	+	+	+	+	+	+	+	-	+	?	-	+	+	-	+	14
Le Berre et al (2014)	+	+	?	+	+	+	?	+	+	+	?	-	+	-	-	+	+	+	+	13
Loeber et al (2009)	+	+	?	+	+	+	+	+	?	-	+	-	+	-	-	+	+	-	+	12
Miranda et al (2009)	+	+	+	+	+	+	+	+	?	+	+	-	+	+	-	+	+	+	+	16
Noel et al (2007)	+	+	?	+	+	+	?	+	+	?	?	-	+	+	-	+	+	-	+	12
Noel et al (2011)	+	+	?	+	+	+	?	+	?	-	+	-	+	-	-	+	+	+	+	12
Salgado et al (2009)	+	+	?	+	+	+	+	+	+	+	+	-	+	-	-	+	+	+	+	15
Tomassini et al (2012)	+	+	?	+	+	+	-	-	?	+	+	-	+	-	-	+	+	?	+	11
Zorlu et al (2013a)	+	+	?	+	+	+	+	+	?	?	+	-	+	-	-	+	+	+	+	13
Zorlu et al (2013b)	+	+	?	+	+	+	?	+	+	+	+	-	+	-	-	+	+	+	+	14

Items 1-19 correspond with Figure X (Quality Criteria Checklist) – Yes = +, No = -, Unclear = ?

APPENDIX 6. CALDICOTT APPROVAL

Lothian NHS Board

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www.nhsllothian.scot.nhs.uk



Ms Louise Young
Trainee Clinical Psychologist
Lothian Substance Misuse Directorate
North East Recovery Hub
Turning Point Leith
5 Links Place
Edinburgh, EH6 7EZ

Date 19th June 2014
Your Ref
Our Ref CG/DF/1401
Enquiries to Caldicott Office
Extension 35452
Direct Line 0131 465 5452
Email Caldicott.Guardian@nhsllothian.scot.nhs.uk

Dear Ms Young

CALDICOTT APPLICATION 1401

Thank you for the information supplied

Request received from	Ms Louise Young
Summary of proposal	The predictive capacity of the ACE-III: Can a cognitive screen help identify those at greater risk of relapse and drop-out from treatment for alcohol dependency
Patient identifiable information requested	Age, Date of Birth, Gender, Other: Information on treatment outcomes, treatment variables (incl substance use status, socio-economic status)
Approved	YES
Advice	Only approved if data is completely anonymised and tabulated. To be transferred to SPSS within the NHS and then directly to a restricted access file on an encrypted University of Edinburgh laptop on an NHS site under appropriate supervision.

Yours sincerely

Professor Alison McCallum
Director of Public Health & Health Policy



Headquarters
Waverley Gate, 2-4 Waterloo Place, Edinburgh EH1 3EG

Chair Mr Brian Houston
Tim Davison, Chief Executive
Lothian NHS Board is the common name of Lothian Health Board

APPENDIX 7. ETHICAL APPROVAL LETTER



SCHOOL of HEALTH IN SOCIAL SCIENCE
CLINICAL PSYCHOLOGY

The University of Edinburgh
Medical School
Doorway 6, Teviot Place
Edinburgh EH8 9AG

Telephone 0131 651 3969
Fax 0131 650 3891
Email submitting.ethics@ed.ac.uk

Louise Young
Trainee Clinical Psychologist

02 October 2014

Dear Louise,

Application for Level 1 Approval

Re: The predictive capacity of the ACE-III: Can a cognitive screen predict treatment engagement and relapse following inpatient detoxification for alcohol dependency?

Thank you for submitting the above research project for review by the Section of Clinical Psychology Ethics Research Panel. I can confirm that the submission has been independently reviewed and was approved on the 25th September 2014.

Should there be any change to the research protocol it is important that you alert us to this as this may necessitate further review.

Yours sincerely,

Kirsty Gardner
Secretary
Clinical Psychology